WATCHMAN™ Left Atrial Appendage Closure (LAAC) Therapy for Patients with Non-Valvular Atrial Fibrillation

Sponsor's Executive Summary

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Terms and Abbreviations

The following terms and abbreviations are used throughout this document:

Term / Abbreviation	Definition
Access System	Access Sheath and Dilator
AE	Adverse Event
AF	Atrial Fibrillation
ASAP	Feasibility study in Europe for new patient population (patients contraindicated for warfarin)
ASD	Atrial Septal Defect
AV Fistula	Arterio-Venous Fistula
AVM	Arterio-Venous Malformation
BI	Barthel Index
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CAP	Continued Access for PROTECT AF continued access registry
CAP2	Continued Access for PREVAIL continued access registry
CEC	Clinical Events Committee
$CHADS_2$ score	Commonly used in medical practice to guide pharmaceutical therapy by targeting the use of anticoagulation or other therapeutic options toward those patients who have the greatest risk of stroke based on history of heart failure, hypertension, age, diabetes, and prior history of stroke
CHA_2DS_2-VASc	A refinement of the $CHADS_2$ score that includes additional risk factors for stroke and adds additional weight to age, female sex, and vascular disease.
CHF	Congestive Heart Failure
Control Group	Patients randomized to receive warfarin therapy
CrI	Credible Interval
CT	Computed Tomography
CV	Cardiovascular
CVA	Cerebrovascular Accident
Delivery System	Delivery Catheter and LAA Closure Device

Term / Abbreviation	Definition
Device Group	Patients who received the WATCHMAN LAAC Therapy
eDFU	Electronic Directions for Use
EDH	Epidural Hemorrhage
Efficacy Primary Endpoint	Within the PREVAIL trial, this is the endpoint that describes the composite of events. (Also referred to as PREVAIL's first primary endpoint).
FDA	Food and Drug Administration
HTN	Hypertension
IDE	Investigational Device Exemption
IND	Investigational New Drug
INR	International Normalized Ratio
IPH/ICH	Intraparenchymal Hemorrhage / Intracerebral Hemorrhage
LAA	Left Atrial Appendage
LAAC	Left Atrial Appendage Closure
LAAOS	Left Atrial Appendage Occlusion Study
LVEF	Left Ventricular Ejection Fraction
Mechanism of Action Primary Endpoint	Within the PREVAIL trial, this is the endpoint that focuses only on ischemic stroke and systemic embolism beyond the seven-day post randomization period. (Also referred to as PREVAIL's second primary endpoint).
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
MRS	Modified Rankin Score
MV	Mitral Valve
NIH	National Institutes of Health
NIHSS	National Institutes of Health Stroke Scale
PFO	Patent Foramen Ovale
PILOT	Feasibility trial of the WATCHMAN device
PMA	Premarket Approval Application
PREVAIL	Second randomized trial
PROTECT AF	First randomized trial

Term / Abbreviation	Definition
Pt-years	Patient Years
RCT	Randomized Control Trial
SAE	Serious Adverse Event
Safety Primary Endpoint	Within the PREVAIL trial, this is the endpoint that characterizes the peri-procedural risk. (Also referred to as PREVAIL's third primary endpoint).
SAH	Subarachnoid Hemorrhage
SAP	Statistical Analysis Plan
SDH	Subdural Hemorrhage
TEE	Transesophageal Echocardiography
TIA	Transient Ischemic Attack
TTE	Transthoracic Echo
TTR	Time in Therapeutic Range
UADE	Unanticipated Adverse Device Effects
US	United States
WATCHMAN LAAC Therapy	The WATCHMAN Access System and Delivery System which permit WATCHMAN Closure Device placement in the LAA via femoral venous access and transseptal septum crossing into the left atrium.

Sponsor's Executive Summary

1 Synopsis

1.1 Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, currently affecting more than 3 million Americans. AF patients have a five-fold increased risk of stroke due to blood stasis from the improperly beating atrium resulting in thrombus formation, which significantly increases the risk for cardioembolic stroke. Ninety-one percent of left atrial thrombi in non-valvular atrial fibrillation have been shown to be isolated to, or originate in, the left atrial appendage[1]. The most common treatment for stroke prevention in AF patients has been long-term warfarin therapy. Despite its proven efficacy, long-term warfarin therapy is not well-tolerated by some patients, has a very narrow therapeutic range, and carries a high risk for bleeding complications.

1.1.1 Indications for Use

The WATCHMAN LAAC Therapy is intended to prevent embolism of thrombus from the left atrial appendage and thus reduce the risk of stroke, systemic embolism, and cardiovascular death in high-risk patients with non-valvular atrial fibrillation who are eligible for warfarin therapy but for whom the risks posed by long-term warfarin therapy outweigh the benefits.

1.1.2 Device Description

The WATCHMAN Left Atrial Appendage Closure (LAAC) Therapy consists of the Access System (Access Sheath and Dilator) and Delivery System (Delivery Catheter and LAA Closure Device). The Access System and Delivery System permit WATCHMAN Closure Device placement in the LAA via femoral venous access and inter-atrial septum crossing into the left atrium. The WATCHMAN Closure Device is a self-expanding nitinol structure with a porous membrane on the proximal face. The Closure Device is constrained within the Delivery System until deployment in the LAA. The Closure Device is available in five sizes ranging from 21 to 33 mm in diameter. The WATCHMAN Closure Device selection is determined by LAA measurements using fluoroscopy and transesophageal echocardiography (TEE).

The WATCHMAN LAA Closure Device is designed to be permanently implanted at, or slightly distal to, the ostium (opening) of the LAA to trap potential emboli before they can exit the LAA. The placement procedure can be done under local or general anesthesia in a catheterization laboratory setting.

1.1.3   Overview of WATCHMAN Clinical Studies

There are currently eight clinical trials completed or underway to evaluate the WATCHMAN LAAC Therapy. Together, the collective human experience within randomized studies and single-arm registries represent a total enrollment of approximately 2000 patients and over 4900 cumulative patient-years of follow-up. Three studies contribute to the analysis in this panel pack and are summarized in Table 1.

Table 1: Clinical Studies in WATCHMAN Program Used to Support Safety and Efficacy in Panel Pack

Study Name	Study Type	Description
PROTECT AF	Randomized	First randomized study
CAP Registry	Continued Access	Continued Access for PROTECT AF
PREVAIL	Randomized	Second randomized study

Five additional studies round out the WATCHMAN clinical program as seen in Table 2. Results from these studies are not used in this panel pack since these studies are either ongoing, studied versions of the WATCHMAN device not under consideration for approval, or studied a patient population other than that for which approval is sought.

Table 2: Clinical Studies in WATCHMAN Program Not Used in Panel Pack

Study Name	Study Type	Description
PILOT	Feasibility	First feasibility trial of the WATCHMAN device
CAP2	Continued Access	Continued access for PREVAIL (this trial is currently enrolling)
ASAP	Feasibility	New patient population (patients contraindicated for warfarin)
EWOLUTION	Post-market	Post-market registry in Europe (this trial is currently enrolling)
WASP	Post-market	Post-market registry in Asia/Pacific (this trial is currently in the start-up phase)

The PROTECT AF results based on 900 patient-years of follow-up were presented at a meeting of the Circulatory System Devices Panel held on April 23, 2009 to discuss and vote on the first premarket approval application for the WATCHMAN LAAC Therapy. The device received a positive committee vote in favor of approval with conditions (7-5) based on the PROTECT AF data.

A second randomized study (PREVAIL) was undertaken to gather additional information. PREVAIL included enrollment milestones for new operators and sites in order to better understand the safety for new operators. PREVAIL also added an additional efficacy endpoint to better characterize the specific mechanism of action of the WATCHMAN Closure Device.

The two randomized studies, PROTECT AF and PREVAIL, form the primary basis of this clinical summary for the determination of safety and efficacy of the WATCHMAN Closure device. An additional study (CAP Registry), which permitted patients to have continued access to the WATCHMAN Closure device after PROTECT AF concluded enrollment (CAP Registry - continued access to PROTECT AF), was a non-randomized registry. The results from the CAP Registry are used to provide supplemental information that show how results, particularly safety, improved over time. Taken together, the results of these studies provide a reasonable assurance of the safety and efficacy of the WATCHMAN Closure Device and demonstrate a favorable benefit/risk profile.

1.2   PROTECT AF, PREVAIL, and CAP Trial Designs

1.2.1   Study Scope

The PROTECT AF and PREVAIL studies were both multicenter, prospective, randomized studies. In both studies, patients were randomly allocated in a 2:1 basis to the WATCHMAN LAAC Therapy or warfarin therapy, respectively. Patients in the PROTECT AF study were drawn from US and European geographies while PREVAIL patients were exclusively from US centers.

A roll-in phase in the PROTECT AF and PREVAIL trials permitted physicians to gain implant experience with the device prior to randomization. All enrolled patients in both groups were required to receive follow-up assessments to re-assess their medical status and evaluate for the occurrence of adverse events. Assessments occur at 45-days, 6-months, 9-months, 12-months and semi-annually thereafter from either the date of randomization for Control patients or the date of the implant procedure for Device patients. Semiannual visits were scheduled through five years (PROTECT AF) or through three years (PREVAIL) and thereafter annually through five years.

The single-arm CAP Registry enrolled patients following the conclusion of the enrollment phase in PROTECT AF and employed the same entry criteria and endpoints as the PROTECT AF trial. The CAP Registry did not have a roll-in phase but followed the same follow-up schedule as PROTECT AF.

1.2.2   Entry Criteria

Patients were eligible to participate in PROTECT AF, PREVAIL, or the CAP Registry if they were at least 18 years of age with non-valvular atrial fibrillation and were eligible for long-term

warfarin therapy with a CHADS$_2$ score of at least 1. An additional criterion was added in PREVAIL in which patients with a CHADS$_2$ score equal to 1 were permitted to enroll only if they met additional risk criteria. This change was done in order to stratify those patients at higher risk for stroke, as recognized by the management guidelines put forth by ACC/AHA/HRS. Additionally, patients taking clopidogrel at the time of screening were excluded from PREVAIL.

1.2.3   Endpoints – PROTECT AF and CAP Registry

It was hypothesized in PROTECT AF that a therapeutic strategy that combined the WATCHMAN Closure device and short-term anti-thrombotic/anti-platelet medications could benefit patients in two ways. The first was by WATCHMAN's mechanism of action, which would reduce the risk of thromboembolic events by preventing the migration of thrombi from the LAA to the body and thereby reduce ischemic strokes and systemic embolism. The second benefit would be derived from the cessation of warfarin, thus sparing patients from the risks of life-long anticoagulation therapy. Accordingly, the efficacy primary endpoint of PROTECT AF was a composite of stroke (ischemic and hemorrhagic), systemic embolism, and cardiovascular/unexplained deaths. The study was designed to compare the event rates in the Device Group to those observed in the Control Group, and analysis was performed with a Bayesian model.

The primary safety endpoint in PROTECT AF was treatment of patients without the occurrence of life-threatening events as determined by the Clinical Events Committee, which included events related to the device and implant procedure as well as events related to the use of warfarin. These events include device embolization requiring retrieval, bleeding events such as pericardial effusion requiring drainage, cranial bleeding events due to any source, gastrointestinal bleeds requiring transfusion, and any bleeding related to the device or procedure that necessitates an operation.

The CAP Registry used the same efficacy and safety endpoints as PROTECT AF.

1.2.4   Endpoints - PREVAIL

The PREVAIL study was intended to gather information to supplement the results from PROTECT AF. The Bayesian analysis of the endpoints of the PREVAIL study was designed to use discounted prior information learned from those patients in the PROTECT AF study meeting the PREVAIL entry criteria. PREVAIL was designed in collaboration with FDA to analyze three primary endpoints. The efficacy primary endpoint was the same efficacy primary endpoint as used in PROTECT AF and consisted of a composite endpoint of ischemic stroke, hemorrhagic stroke, systemic embolism, or cardiovascular/unexplained death.

The mechanism of action primary endpoint in PREVAIL focused on those outcomes believed to be due to the specific mechanism of action of the WATCHMAN device once a seven day period of peri-procedural risk had passed, namely the WATCHMAN Closure Device's ability to prevent thromboembolic events by sealing off the left atrial appendage as a source for thrombi. This endpoint was defined to include ischemic stroke or systemic embolism excluding the first 7 days post randomization.

The safety primary endpoint was intended to characterize major safety events associated with the implant procedure by capturing the incidence of serious events occurring within the seven day period of peri-procedural risk. This safety endpoint defined safety as the percentage of patients who experienced one of the following events between the time of randomization and within 7 days of the procedure or by hospital discharge, whichever is later: all-cause death, ischemic stroke, systemic embolism, or device or procedure related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair. Percutaneous catheter drainage of pericardial effusions, snaring of an embolized device, thrombin injection to treat femoral pseudoaneurysm, and non-surgical treatments of access site complications were excluded from this endpoint.

For simplicity, this panel pack will use the following nomenclature to describe the endpoints of the PREVAIL study:

- *Efficacy Primary Endpoint: The endpoint that describes the composite of events (first primary endpoint).*

- *Mechanism of Action Primary Endpoint: The endpoint that focuses only on ischemic stroke and systemic embolism beyond the seven-day post randomization period (second primary endpoint).*

- *Safety Primary Endpoint: The endpoint that characterizes the peri-procedural risk (third primary endpoint).*

1.2.5 Statistical Analysis Plan

The statistical analysis plan for PROTECT AF allowed sequential evaluations of the statistical objectives under a Bayesian model. For PREVAIL, an adaptive design with a flexible sample size and historical prior based on those patients from PROTECT AF meeting PREVAIL eligibility criteria was used. Predictive probabilities for study success were calculated 6 months after enrollment completion. The CAP Registry did not have a control group and the efficacy and safety endpoints were to be summarized the descriptive statistics rather than analytical statistics.

1.2.6 Study Flow

For all studies, patients were screened and those who met all of the entry criteria underwent transesophageal echocardiography (TEE) to characterize the anatomy of the left atrial appendage and examine it for the presence of thrombi. If the TEE was clear, patients were randomized to either control (warfarin) or device (WATCHMAN).

For PROTECT AF and PREVAIL, patients randomized to the Control Group had their dose of warfarin adjusted to try to maintain an INR between 2.0 and 3.0 for the duration of the study. Patients randomized to the Device Group underwent an implant procedure. Those patients not successfully implanted were maintained on warfarin and followed for acute events, but long-term follow-up was not specified in the protocol. Those patients successfully implanted with a WATCHMAN Closure device were maintained on warfarin and aspirin until the 45 day visit and re-evaluated with TEE.

At 45 days, if the seal around the device was adequate, warfarin was discontinued, higher dose aspirin was recommended, and clopidogrel was added. After six months, clopidogrel was discontinued and patients were recommended to continue high dose aspirin indefinitely. If the seal around the device was inadequate at 45 days, patients were maintained on a combination of low dose aspirin and warfarin. If the seal was still inadequate beyond six months, it was recommended that low dose aspirin be given in combination with warfarin until an adequate seal could be determined. Once warfarin was discontinued, patients were recommended to continue high dose aspirin indefinitely.

Table 3 summarizes key elements of the two randomized controlled trials.

Table 3: Summary: Comparison of the PROTECT AF and PREVAIL Studies

Characteristic	PROTECT AF	PREVAIL
Study Design	Randomized controlled trial 2:1 randomization Device/Control	Same
Patients / Centers	800 patients 59 US and European centers	461 patients 41 US sites
Key Entry Criteria	Age $\geq$ 18 Documented non-valvular AF Eligible for long-term warfarin Eligible for warfarin cessation if LAA is sealed	Same
	Clopidogrel use permitted	Clopidogrel use excluded if within 7 days prior to implant
	CHADS$_2$ Score $\geq$ 1	CHADS$_2$ Score $\geq$ 2 OR CHADS$_2$ Score =1 with conditions[◊]
Efficacy Primary Endpoint	Composite of: • Ischemic stroke • Hemorrhagic stroke • Systemic embolism • Cardiovascular/unexplained death	Same
Mechanism of Action Primary Endpoint	Not applicable	Occurrence of ischemic stroke or systemic embolism > 7 days
Safety Primary Endpoint	Freedom from occurrence of life-threatening events as determined by the Clinical Events Committee[**]	Occurrence of specific events[*] within 7 days of the procedure or discharge
	Evaluated in both Device and Control Groups	Evaluated in Device Group only
Study Oversight	• Clinical Events Committee • Data and Safety Monitoring Board	Same

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[◊] Conditions include any one of the following: Female age 75 or older, has a baseline LVEF between 30-35%, is age 65-74 <u>and</u> had diabetes or coronary artery disease, or is age 65 or greater <u>and</u> has congestive heart failure

[**] Included events such as device embolization requiring retrieval, bleeding events such as pericardial effusion requiring drainage, cranial bleeding events due to any source, gastrointestinal bleeds requiring transfusion and any bleeding related to the device or procedure that necessitates an operation.

[*] All-cause death, ischemic stroke, systemic embolism, or device or procedure related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair. Percutaneous catheter drainage of pericardial effusions, snaring of an embolized device, thrombin injection to treat femoral pseudoaneurysm, and non-surgical treatments of access site complications were excluded from this endpoint.

1.3 PROTECT AF, PREVAIL, and CAP Study Results

1.3.1 Overview

In PROTECT AF, a total of 800 patients were enrolled at 55 centers in the United States and 4 centers in Europe from February 14, 2005 through June 30, 2008. Of these, 707 patients were randomized patients (463 WATCHMAN and 244 warfarin control) and 93 were non-randomized roll-in device patients.

The most recent PROTECT AF dataset presented in this document includes data through a mean follow-up of 3.8 years of follow-up, representing an accumulation of 2621 patient-years of follow-up. The analysis presented to the Advisory Panel in 2009 included PROTECT AF data collected through 900 patient-years of follow-up with a mean follow-up of 1.3 years.

In PREVAIL, a total of 461 patients were enrolled at 41 centers in the United States from November 1, 2010 through June 28, 2012. Of these, 407 patients were randomized patients (269 WATCHMAN and 138 warfarin control) and 54 were non-randomized roll-in device patients. Patients continue to be followed through their 5 year follow-up visit at the time of this report. The current analysis includes PREVAIL data through January 16, 2013 which constitutes a minimum of six months of follow-up and a cumulative follow-up of 400 patient-years.

As part of the PREVAIL Investigational Device Exemption (IDE) submission, the PROTECT AF data were updated to reflect 1588 patient-years of follow-up. The statistical analysis associated with this follow-up period for the patients who would have met PREVAIL entry criteria provides the prior information used for the PREVAIL analysis.

A total of 566 CAP patients were enrolled at 24 sites in the United States and two in Europe and have been followed for a mean of 2.4 years. Patients continue to be followed through their 5-year follow-up visit at the time of this report. This study was a single-arm observational study and all patients were assigned to receive a WATCHMAN device.

1.3.2 Demographics

The PROTECT AF and PREVAIL populations had similar distributions for sex and race/ethnicity as shown in Table 4. PREVAIL enrolled patients who were older and at greater risk of stroke. This difference was by design to enroll a population at higher risk compared to the PROTECT AF population.

Table 4: Summary: Baseline Demographic and Clinical Characteristics

Characteristic	PROTECT AF N=707	PREVAIL N=407	CAP Registry N=566
Age (years)	72.0 ± 8.9	74.3 ± 7.4	74.0 ± 8.3
Gender (Male)	497 (70.3%)	285 (70.0%)	371 (65.5%)
Race/Ethnicity (%)			
Asian	5/707 (0.7%)	2/407 (0.5%)	9/566 (1.6%)
Black/African American	11/707 (1.5%)	7/407 (1.7%)	11/566 (1.9%)
Caucasian	647/707 (91.5%)	384/407 (94.3%)	520/566 (91.9%)
Hispanic/Latino	40/707 (5.7%)	11/407 (2.7%)	20/566 (3.5%)
Other	4/707 (0.6%)	3/407 (0.7%)	6/566 (1.1%)
$CHADS_2$ Score (as a continuous variable)	2.2 ± 1.2	2.6 ± 1.0	2.5 ± 1.2
$CHADS_2$ Risk Factors			
Congestive heart failure	190 (26.9%)	95 (23.3%)	108 (19.1%)
Hypertension	635 (89.8%)	372 (91.4%)	502 (88.8%)
Age ≥ 75	305 (43.1%)	218 (53.6%)	293 (51.8%)
Diabetes	185 (26.2%)	132 (32.4%)	141 (24.9%)
Stroke/TIA	131 (18.5%)	113 (27.8%)	172 (30.4%)
Aspirin Use	416 (58.8%)	200 (49.1%)	---

1.3.3   Patient Status

1.3.3.1 Patient Accountability

The flow of enrolled patients throughout the WATCHMAN studies is shown in Figure 1 and patient accountability through study entry for the PROTECT AF and CAP Registry is depicted in Figure 2. Patient accountability for PREVAIL is shown in Figure 3.

Figure 1: Summary: Study Flow
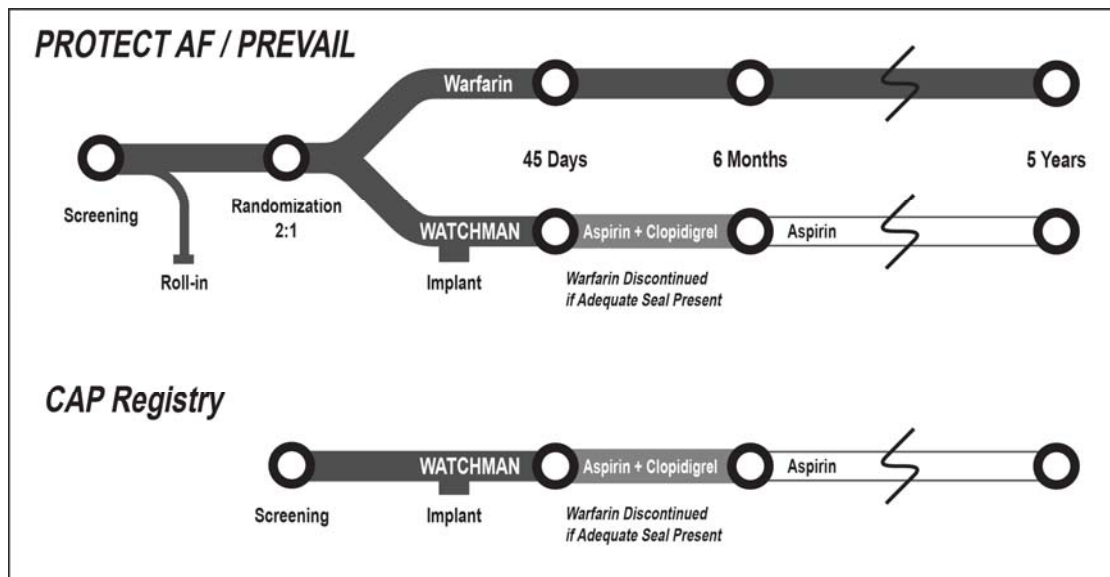
Figure 2: Summary: Patient Accountability – PROTECT AF and CAP
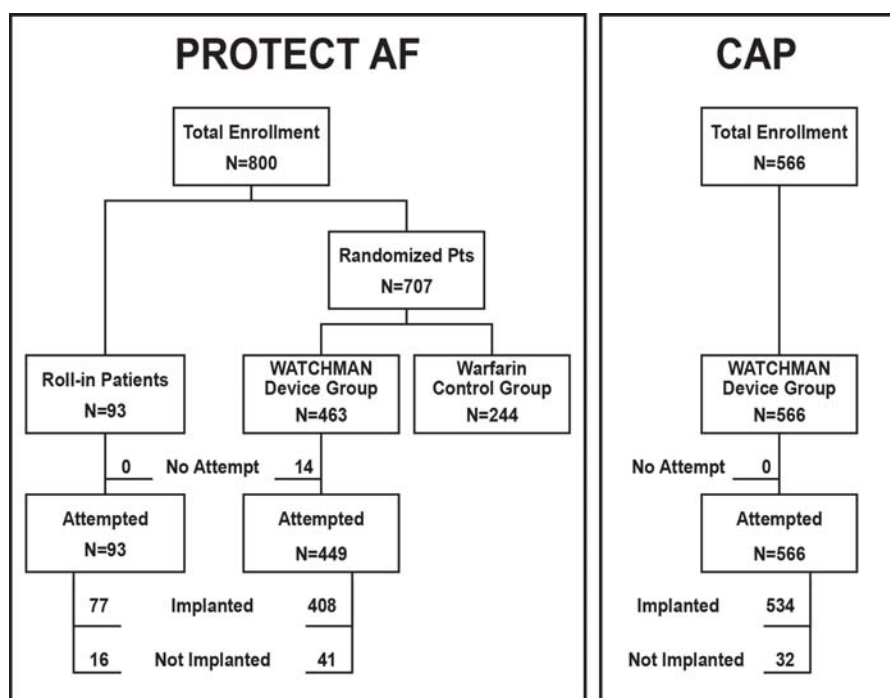
Figure 3: Summary: Patient Accountability - PREVAIL
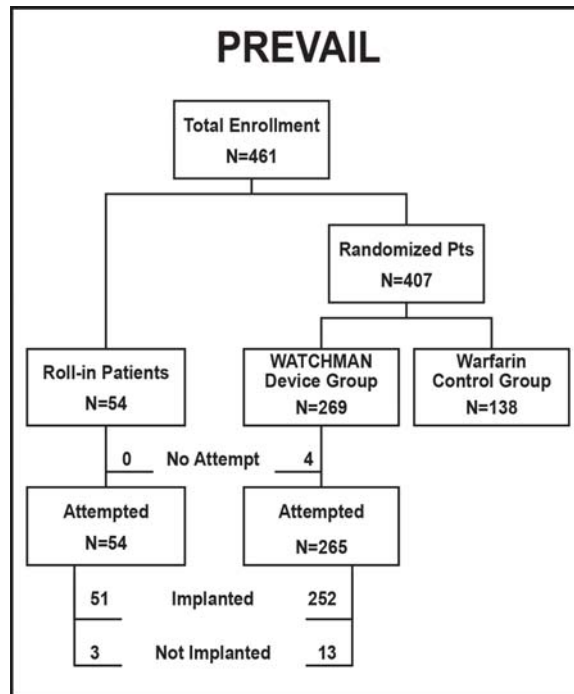
1.3.3.2 Patient Status as of Data Lock

The status of enrolled patients for the three studies is detailed in Table 5.

Table 5: Summary: Patient Status

Status	PROTECT AF		PREVAIL		CAP Registry (N=566)
	Device (N=463)	Control (N=244)	Device (N=269)	Control (N=138)	
Completed Five Years	202 (43.6%)	92 (37.7%)	0	0	0
Active as of Data Lock	111 (24.0%)	42 (17.2%)	233 (86.6%)	123 (89.1%)	456 (80.6%)
Death	57 (12.3%)	44 (18.0%)	13 (4.8%)	5 (3.6%)	53 (9.4%)
Lost to Follow-up	13 (2.8%)	11 (4.5%)	2 (0.7%)	1 (0.7%)	10 (1.8%)
Patient Consent Withdrawn	17 (3.7%)	45 (18.4%)	2 (0.7%)	8 (5.8%)	10 (1.8%)
Other	12 (2.6%)	10 (4.1%)	2 (0.7%)	1 (0.7%)	5 (0.9%)
No Device Implanted	51 (11.0%)	N/A	17 (6.3%)	N/A	32 (5.7%)

1.3.4   Implant Procedure

In PROTECT AF, a successful implant, defined as deployment and release of the device into the left atrial appendage, occurred in 90.9% (408/449) of patients for whom an implant procedure

was attempted. When compared to the PROTECT AF study, improvements in the implant success rate were observed in the CAP Registry [534/566 (94.3%)] and PREVAIL [252/265 (95.1%)].

Procedure times were similar between the two studies for successfully implanted patients with a mean time of 57.4 ± 30.4 minutes for PROTECT AF and a mean time of 58.6 ± 26.6 minutes for PREVAIL. Mean procedure time was not collected in the CAP Registry.

1.3.5   *Warfarin Cessation*

The intent of the therapeutic strategy of the WATCHMAN LAA Closure Device is to permit discontinuation of warfarin once an adequate seal has been established[2]. In the WATCHMAN studies, warfarin could be discontinued if echocardiographic evidence of an adequate seal was present at 45 days. If the seal was not found to be adequate at 45 days, TEE was repeated at six months and again at 12 months if necessary to confirm occurrence of the seal. In all three studies, as shown in Table 6, investigators were able to discontinue warfarin by 45 days in at least 86% of patients and in 93% or more by 12 months, indicating that this goal is met in a high proportion of patients.

Table 6: Summary: Successful Warfarin Cessation in Patients Implanted with the WATCHMAN Closure Device by Study

Visit	PROTECT AF	PREVAIL	CAP
	N/Total (%)	N/Total (%)	N/Total (%)
45 Day	348/401 (86.8%)	227/246 (92%)	507/529 (95.8%)
6 Month	355/385 (92.2%)	235/239 (98%)	493/500 (98.6%)
12 Month	345/370 (93.2%)	141/142 (99%)	455/472 (96.4%)

1.4   Efficacy Primary Endpoint – PROTECT AF

The PROTECT AF and PREVAIL randomized studies and the CAP Registry all had a common efficacy primary endpoint consisting of a composite of stroke (ischemic or hemorrhagic), systemic embolism or cardiovascular/unexplained death.

The PROTECT AF efficacy endpoint presented at the 2009 panel based on 900 patient-years of follow-up met its pre-specified criterion for non-inferiority. The WATCHMAN device was associated with a rate ratio from the Bayesian analysis of 0.68 [95% CrI (0.37, 1.41)] and a posterior probability of 0.998 for non-inferiority. Since that panel meeting, more follow-up data are available to 2621 patient-years of follow-up. The rate ratio based on the current data set was 0.60 [95% CrI (0.40, 1.05)]. Not only was the non-inferiority criterion satisfied with a posterior

probability >0.999, but superiority was also achieved with the WATCHMAN Closure Device when compared to warfarin (posterior probability of 0.960).

The efficacy primary endpoint results are illustrated in Figure 4 for the composite as well as the individual components as well as a tabulation of events in Table 7 for the current data set. The PROTECT AF study was not designed to detect differences within each component, but examination of these results may give additional insight into how they contributed to the overall result.

Figure 4: Summary: PROTECT AF Efficacy Primary Endpoint: Stratified by Component
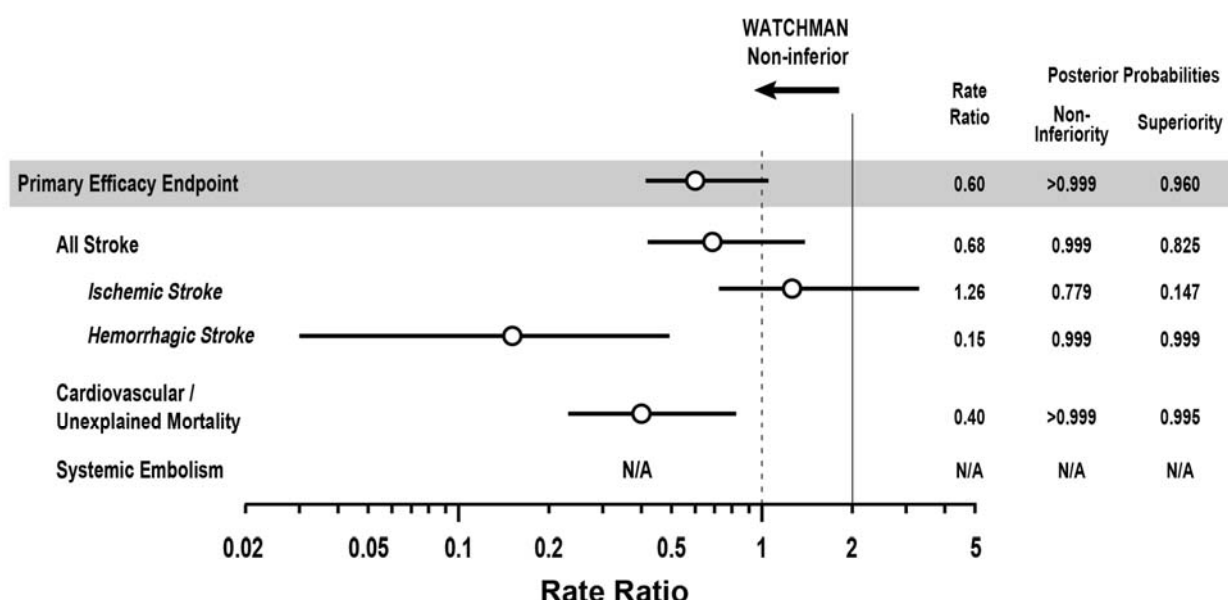
Table 7: Summary: Events Contributing to the Efficacy Primary Endpoint in PROTECT AF Study at 2621 Patient-Years

Type	PROTECT AF 2621 Patient-Years	
	Device (N=463) (N Events/%)	Control (N=244) (N Events/%)
Stroke – Ischemic	24 (5.2%)	10 (4.1%)
Stroke – Hemorrhagic	2 (0.4%)	10 (4.1%)
Systemic Embolism	2 (0.4%)	0 (0.0%)
Death – Cardiovascular and Unexplained	11 (2.4%)	14 (5.7%)
Total	39 (8.4%)	34 (13.9%)

The WATCHMAN Closure Device was non-inferior to warfarin in reducing the rate of stroke from any cause. These results were primarily driven by a statistically significant reduction in the relative risk of hemorrhagic stroke by 85% (posterior probability for superiority = 0.999). The Device Group was also experienced a 60% reduction in the relative risk of cardiovascular or unexplained death (posterior probability for superiority = 0.995).

To put these rates into historical perspective over the progression of the PROTECT AF study, the rate ratios over the progression of the PROTECT AF study as measured at the 900-, 1588- and 2621 patient-year intervals are shown below in Table 8.

Table 8: Summary: PROTECT AF: Efficacy Primary Endpoint: Results by Patient-Year Intervals

Analysis Cohort	Device		Control		Rate Ratio (95% CrI)		Posterior Probabilities	
	Rate (95% CrI)		Rate (95% CrI)				Non-inferiority	Superiority
900 pt-years	3.4	(2.1, 5.2)	5.0	(2.8, 7.6)	0.68	(0.37, 1.41)	0.998	0.837
1588 pt-years	3.0	(2.1,4.3)	4.3	(2.6, 5.9)	0.71	(0.44, 1.30)	>0.999	0.846
2621 pt-years	2.3	(1.7, 3.2)	3.8	(2.5, 4.9)	0.60	(0.41, 1.05)	>0.999	0.960

The Kaplan-Meier curves in Figure 5 illustrate the event rates for the two treatment groups as they accrue over time. The set of curves in the upper panel depict the results based on 900 patient-years in which the curves separate after about one year. The long-term follow-up data from PROTECT AF at 2621 patient-years of follow-up are shown in the lower panel, which indicate that the effect is not only preserved but extended. The Kaplan-Meier curves continue to diverge, underscoring the long-term efficacy of the WATCHMAN Closure Device as a non-inferior alternative to warfarin.

Figure 5: Summary: PROTECT AF: Efficacy Primary Endpoint: Kaplan-Meier Curves at 900 and 2621 Patient-Years

PROTECT AF
(900 Patient-Years)

Mean follow-up = 1.3 years

| 463 | 270 | 92 | 22 | WATCHMAN |
| 244 | 147 | 52 | 12 | Control |

PROTECT AF
(2621 Patient-Years)

89.9%

82.2%

Mean follow-up = 3.8 years

| 463 | 382 | 360 | 337 | 317 | 196 |
| 244 | 218 | 200 | 173 | 147 | 87 |
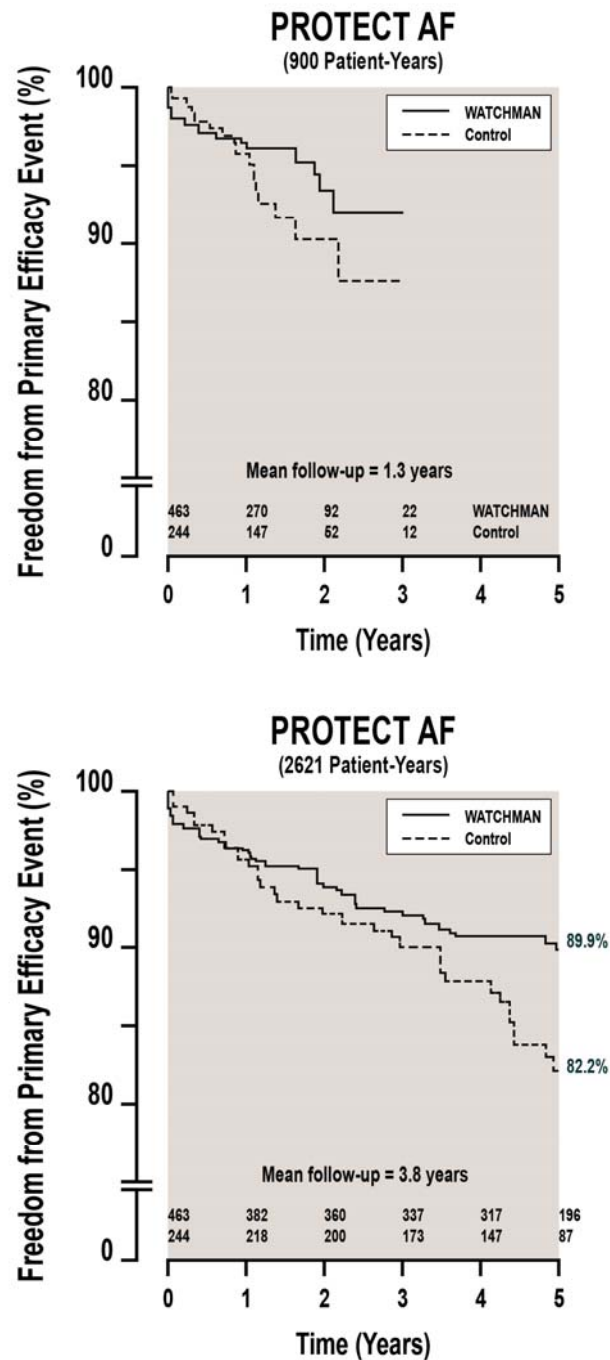
1.4.1 Efficacy Primary Endpoint – PREVAIL

In PREVAIL, there were 14 endpoint events among the 269 patients in the Device Group and 4 events among the 138 patients in the Control Group as detailed in Table 9.

Table 9: Summary: PREVAIL: Efficacy Primary Endpoint Events

Type	PREVAIL	
	Device (N Events/%)	Control (N Events/%)
Stroke - Ischemic	5 (1.9%)	1 (0.7%)
Stroke - Hemorrhagic	1 (0.4%)	0 (0.0%)
Systemic embolism	1 (0.4%)	0 (0.0%)
Death – Cardiovascular and Unexplained	7 (2.6%)	3 (2.2%)

The Bayesian analysis revealed that the 18-month rate ratio was 1.07 [95% CrI (0.57, 1.89)]. The upper boundary exceeded the non-inferiority margin of 1.75 and therefore did not meet the condition for non-inferiority.

The temporal pattern of efficacy primary endpoint events are plotted as Kaplan-Meier curves for the PREVAIL study as shown in Figure 6.

Figure 6: PREVAIL: Efficacy Primary Endpoint – Kaplan-Meier Curves
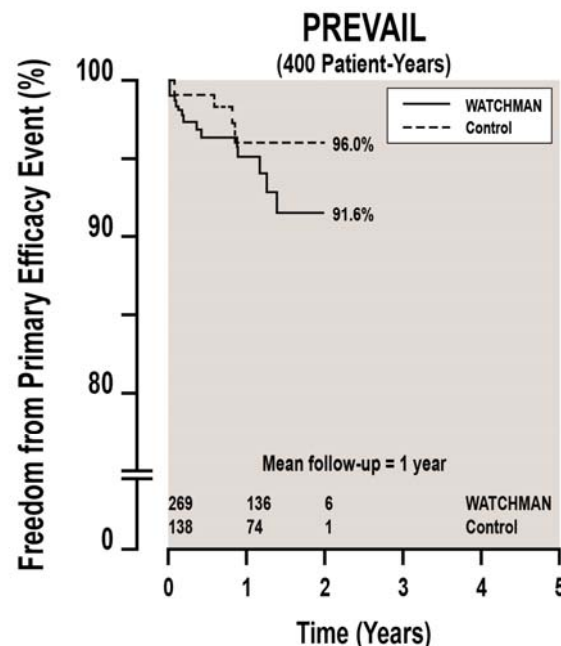
1.4.2 Efficacy Primary Endpoint – Aggregate of PROTECT AF and PREVAIL with Reference to CAP Registry

Although Bayesian analyses were the pre-specified analyses for the PROTECT AF and PREVAIL studies, it may be interesting to take a purely descriptive approach without any Bayesian priors. This section provides a supplementary analysis that aggregated the individual patient data from the two randomized trials into a single set of Kaplan-Meier curves. As the two randomized trials were designed utilizing Bayesian methodologies, no predefined statistical conclusions can be drawn from this analysis, which is intended for illustrative purposes.

The CAP Registry, which was not randomized but used the same efficacy primary endpoint, is not aggregated with the two randomized studies but the efficacy data are also shown for illustrative purposes.

The upper left panel in Figure 7 depicts the efficacy primary endpoint for the PROTECT AF and PREVAIL WATCHMAN device arms and the CAP Registry results individually. The upper right panel in Figure 7 illustrates the warfarin control arms from the PROTECT AF and PREVAIL studies. The set of Kaplan-Meier curves in the lower center panel of Figure 7 shows the two Device Group arms combined and plotted against the two Control Group arms combined. The CAP Registry arm was not included in this final plot.

Figure 7: Efficacy Primary Endpoint: Aggregate of PROTECT AF and PREVAIL Randomized Trials and CAP Registry Outcome
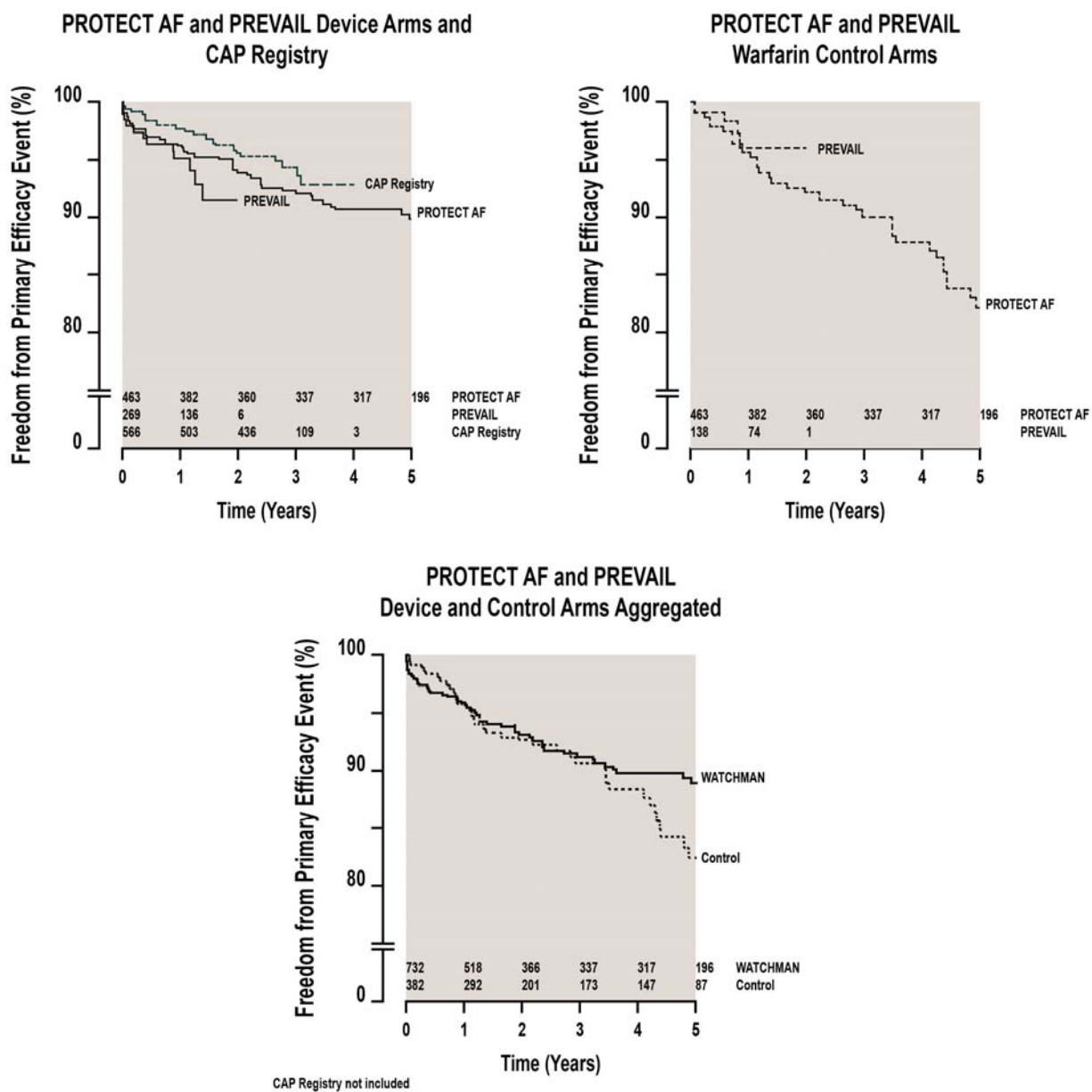
> - *The long-term PROTECT AF data with 2621 patient-years of follow-up demonstrated that efficacy in the Device Group met the condition for non-inferiority when compared to the Control Group and demonstrated superiority as well.*
>
> - *PREVAIL did not demonstrate non-inferiority of primary efficacy of the Device Group compared to the Control Group.*
>
> - *Aggregate analysis of PROTECT AF and PREVAIL reinforce non-inferiority of the WATCHMAN Closure Device to warfarin.*

1.5   Mechanism of Action Primary Endpoint

PREVAIL had a mechanism of action primary endpoint that focused exclusively on ischemic stroke and systemic embolism rates. In the Device Group, there were 5 events classified as an ischemic stroke or systemic embolism out of 269 patients compared to 1 event out of 138 patients in the Control Group, corresponding to 18-month model rates of 0.0253 and 0.0200, respectively. The 18-month absolute rate difference was 0.0053 with a 95% CrI of (-0.0190, 0.0273). This result met the non-inferiority criterion pre-defined in the statistical analysis plan which required the 18-month rate difference to have a 95% upper credible interval less than 0.0275. The plan also allowed for non-inferiority of the second primary endpoint if the 18-month rate ratio had a 95% upper credible interval less than 2.0.

Non-inferiority of the Device Group to the Control Group was achieved for the mechanism of action primary endpoint of ischemic stroke or systemic embolism greater than 7 days post randomization, which corroborates the findings from PROTECT AF that the WATCHMAN LAA Closure Device and warfarin exerted similar effects in reducing stroke.

The mechanism of action primary endpoint was met in PREVAIL and demonstrated non-inferiority of the WATCHMAN device compared to warfarin for prevention of ischemic stroke and systemic embolism.

1.6   Safety

In PROTECT AF, the primary safety endpoint was defined as freedom from occurrence of life-threatening events as determined by the Clinical Events Committee.[**] By design this includes long term complications of therapy as well as acute procedural events. After 2621 patient-years of follow-up, the event rate was 3.6% per 100 patient-years of follow-up for the Device Group

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[**] Included events such as device embolization requiring retrieval, bleeding events such as pericardial effusion requiring drainage, cranial bleeding events due to any source, gastrointestinal bleeds requiring transfusion and any bleeding related to the device or procedure that necessitates an operation.

and 3.1% per 100 patient-years of follow-up for the Control Group, yielding a rate ratio of 1.17 [95% CrI (0.78, 1.96)]. This outcome indicated that risks in the Device Group in the long term were comparable to those seen in the Control Group. Procedure related life-threatening events in the Device Group included cardiac perforations requiring surgical repair 7/449 (1.6%), pericardial effusion with tamponade requiring percutaneous drainage 13/449 (2.9%), device embolization 3/449 (0.7%), and procedure related ischemic stroke 5/449 (1.1%).

The Kaplan-Meier curves for time to a safety event are illustrated in the figure below. In the Device Group, the events are concentrated early, around the time of the procedure. In contrast, patients in the Control Group have a constant exposure to the risk of warfarin that eventually catches up to the rate observed in the Device Group as shown in Figure 8.

Figure 8: PROTECT AF: Safety - Kaplan-Meier Curves
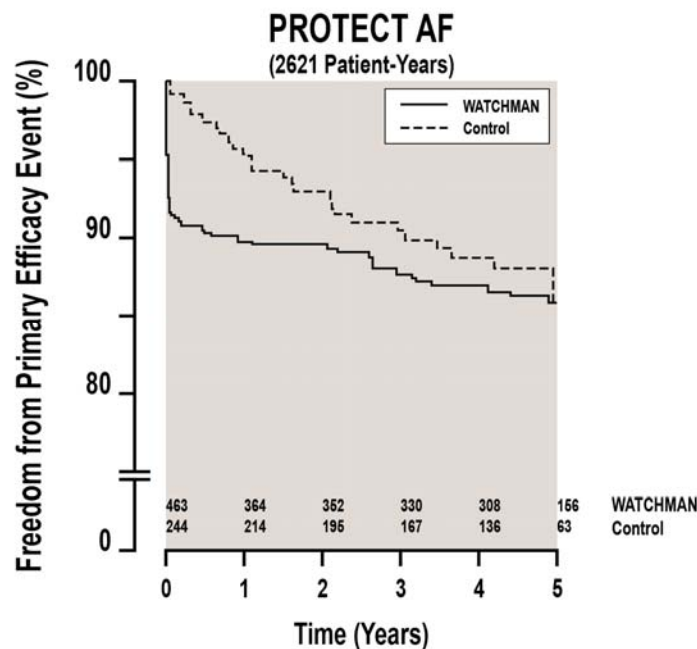
Many of these procedural complications were observed early in the study when the implant technique and device placement were novel. There was a 9.9% rate of procedure-related safety events among the 232 patients enrolled in the first half of the study. Revision of the training program, alterations to the implant procedure, and technical improvements led to a reduction in safety event rates. The rate of procedure-related safety events was cut in half to 4.8% among the 231 patients enrolled in the second half of the study.

The CAP Registry, which provided continued access to the WATCHMAN LAAC Therapy following PROTECT AF, included the following procedure related complications: cardiac perforations requiring surgical repair 1/566 (0.2%), pericardial effusion with tamponade requiring percutaneous drainage 7/566 (1.2%), device embolization 1/566 (0.2%), and no procedure related ischemic stroke. The CAP Registry underscored the durability of the changes

previously described that were implemented in PROTECT AF. The rate of procedure-related safety events was 4.1%, similar to that observed in the second half of PROTECT AF's enrollment.

In PREVAIL, the primary safety endpoint was defined as the occurrence of pre-specified safety events[*] within 7 days of the procedure or discharge. Success for this endpoint was achieved if the percentage of patients experiencing one of the events was statistically less than the performance goal, defined as 2.67%, with an upper bound of the one-sided 95% credible interval less than the performance goal. There were six (6) events meeting the primary safety endpoint definition in 269 patients. The six events consisted of two device embolizations (0.7%), one arterio-venous (AV) fistula (0.4%), one cardiac perforation (0.4%), one pericardial effusion with cardiac tamponade (0.4%), and one major bleed requiring transfusion (0.4%). Therefore, 2.2% of patients experienced an event and a one-sided 95% credible interval upper bound was 2.652%. Since the upper bound was within the performance goal of 2.67%, the condition for safety was satisfied.

> *PREVAIL met its safety endpoint by demonstrating that the 2.2% safety event rate's upper 95% credible interval of 2.652% was within the performance goal of 2.67%.*

The PREVAIL study required a minimum randomized enrollment of 20% of patients by new sites and 25% of patients by new operators. New operators could participate at either new or experienced institutions.

There were 38.8% (158/407) randomized patients enrolled by new sites, surpassing the 20% protocol requirement; and 39.1% (159/407) randomized patients enrolled by new operators surpassing the 25% protocol requirement.

Of the six primary safety endpoint events, 2/105 (1.9%) occurred with new operators and 4/164 (2.4%) were reported with experienced operators. There was no statistically significant difference in these rates (p=1.00, Fisher's exact test). These results from the PREVAIL study indicated new operators could perform the implant procedure without increased risk when compared to experienced operators.

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[*] All-cause death, ischemic stroke, systemic embolism, or device or procedure related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair. Percutaneous catheter drainage of pericardial effusions, snaring of an embolized device, thrombin injection to treat femoral pseudoaneurysm, and non-surgical treatments of access site complications were excluded from this endpoint.

With the training program used in PREVAIL, new operators performed the implant without increased risk compared to experienced operators.

1.7   Conclusions

The totality of the data available with the WATCHMAN device from long-term results of the PROTECT AF study supplemented by the results of the CAP Registry and PREVAIL trial provides reasonable assurance of the safety and efficacy of the WATCHMAN LAAC Therapy to prevent embolism of thrombus from the left atrial appendage and thus reduce the risk of stroke, systemic embolism, and cardiovascular death in high risk patients with non-valvular atrial fibrillation who are eligible for warfarin therapy but for whom the risk posed by long term warfarin therapy outweigh the benefits.

1.7.1   Efficacy

The efficacy of the WATCHMAN Closure Device in preventing thromboembolic events and cardiovascular death has been demonstrated.

- ***Investigators were able to implant the device with a high degree of success***. Implant success rates have increased from 90.9% in PROTECT AF to 94.3% in the CAP Registry and 95.1% in PREVAIL.

- ***Patients were able to successfully cease the use of warfarin***. By 45 days, warfarin cessation occurred in at least 87% of patients successfully implanted with the device. This figure improved to at least 93% at one year.

- ***The PROTECT AF study met its efficacy primary endpoint of non-inferiority when comparing the WATCHMAN Closure Device to warfarin, eventually reaching superiority***. This endpoint was a composite of ischemic stroke, hemorrhagic stroke, systemic embolism, or death due to cardiovascular or unknown causes encompassing 2621 patient-years of follow-up. PROTECT AF demonstrated a 40% reduction in the risk of a primary endpoint event [rate ratio= 0.60, 95% CrI (0.41, 1.05), posterior probability >0.999 for non-inferiority, 0.960 for superiority].

- ***The PREVAIL study did not meet the efficacy primary endpoint***. This endpoint was the same as in PROTECT AF. The rate ratio was 1.07, CrI (0.57, 1.89) with a posterior probability of 0.958.

- ***The WATCHMAN Closure Device is non-inferior to warfarin in reducing events due to ischemic stroke or systemic embolism (mechanism of action primary endpoint).*** In

the PREVAIL study, the WATCHMAN Closure Device met its mechanism of action endpoint when compared to warfarin. The 18-month rate difference was 0.0053 with a 95% CrI of (-0.0190, 0.0273), which was within the non-inferiority margin of 0.0275 with a posterior probability of 0.978.

1.7.2 Safety

The safety of the WATCHMAN LAAC Therapy has been shown across the studies in the WATCHMAN clinical program.

- ***A substantial improvement in safety was seen early in the WATCHMAN clinical experience.*** The rate of safety events was reduced from the early PROTECT AF enrollment period to the late PROTECT AF enrollment period. Changes in training, the implant procedure, and technical aspects of the WATCHMAN device reduced the rate of safety events from 9.9% in the first half to 4.8% in the second half. The durability of this effect was evident in the CAP Registry in which the safety event rate was 4.1%.

- ***The safety endpoint in the PREVAIL study was met.*** The event rate was 2.2% with a 95% credible interval bound of 2.65%, within its pre-specified performance goal of 2.67%.

- ***Reductions in specific procedure-related events were observed over the progression of studies.*** From the PROTECT AF study through PREVAIL, the rates of cardiac perforations requiring surgery, pericardial effusion with tamponade, and procedure-related ischemic strokes declined. The rate of device embolization was small and consistent across the studies.

- ***The training program employed in PREVAIL was successful.*** The risk associated with the implant procedure was similar for both new and experienced operators.

<u>Summary</u>

The totality of the data available on the WATCHMAN device, from the initial PROTECT AF study, supplemented by the results of the CAP Registry and the PREVAIL trial consistently provides reasonable assurance of the safety and efficacy of the WATCHMAN LAAC Therapy

The WATCHMAN Closure Device can be safely implanted by trained operators to prevent embolism of thrombus from the left atrial appendage and reduce the risk of stroke, systemic embolism, and cardiovascular death in high risk patients. Between 87-96% of successfully implanted patients could discontinue the use of warfarin after 45 days. The primary efficacy endpoint was met in PROTECT AF and demonstrated superiority of the WATCHMAN device to warfarin. The totality of the data from these studies continues to support the findings that the WATCHMAN LAAC Therapy is safe and effective.

2 Background and Clinical Need

2.1 Background

Atrial fibrillation (AF) is one of the most common rhythm disturbances, affecting approximately 5.5 million people worldwide, including approximately 10% of people older than 75 years[3]. Atrial fibrillation can cause stagnation of blood and subsequent thrombosis in the left atrial appendage, resulting in the most debilitating consequence of AF: thromboembolism and stroke. The rate of ischemic stroke attributed to non-valvular AF is estimated as an average of 5% per year which is 2-7 times that of people without AF[4].

Treatment with the oral vitamin K antagonist warfarin for the prevention of thromboemboli originating in the left atrial appendage has been well documented[5,6,7]. It is effective and considered the gold standard treatment for patients with non-valvular AF for prevention of stroke. While warfarin therapy has formed part of standard treatment for many years, there are numerous challenges with the therapy which may limit its long-term use, such as frequent need for monitoring and dosage adjustments, dietary and metabolic interactions, and concerns surrounding patient compliance. The potential for serious and fatal bleeding events are of high concern for patients and caregivers, combined with high frequency nuisance bleeds (nose bleeds, GI bleeding), resulting in this drug frequently not being well tolerated long-term.

Echocardiography has demonstrated the left atrial appendage (LAA) to be a major source of thrombus in patients with atrial fibrillation.[1,8] While the risk of stroke increases with age and the disability and tolerance concerns with available pharmaceutical therapy persist, the need for ongoing protection against thromboembolic complications remains unmet. Boston Scientific has investigated the use of a permanent implantable device, WATCHMAN, to close the opening of the left atrial appendage, the location where the vast majority of thrombi originate. This device may provide an alternative to warfarin therapy in patients with non-valvular AF who require thromboembolic protection and are eligible for warfarin therapy but for whom the risks posed by long-term warfarin therapy outweigh the benefits.

2.2 Risk Factors for Stroke

The most widely recognized tool for assessing the risk of stroke in patients with AF at the time of initiation of the pivotal study was the CHADS$_2$ risk stratification scheme.[9] The CHADS$_2$ score was commonly used in medical practice to guide pharmaceutical therapy by targeting the use of anticoagulation or other therapeutic options toward those patients who have the greatest risk of stroke.

A CHADS$_2$ score is calculated based upon elements in the medical history utilizing a point system that assigns one point each for congestive heart failure, hypertension, age $\geq$ 75 years, and diabetes, and assigns two points for a previous stroke or TIA. The higher the CHADS$_2$ score, the

greater the risk of developing stroke. Specifically, the risk of stroke based upon the $CHADS_2$ score is located in Table 10.

Table 10: Expected Stroke Rate Based on $CHADS_2$ Score[9]

$CHADS_2$ Score	Adjusted Stroke Rate* (95% CI)
0	1.9 (1.2-3.0)
1	2.8 (2.0-3.8)
2	4.0 (3.1-5.1)
3	5.9 (4.6-7.3)
4	8.5 (6.3-11.1)
5	12.5 (8.2-17.5)
6	18.2 (10.5-27.4)

*The adjusted stroke rate is the expected stroke rater per 100 patient-years from the exponential survival model, assuming that aspirin was not taken.

The $CHADS_2$ score has undergone refinement that added additional risk factors and changed the weighting behind age such that patients aged 75 or greater had two points and female sex and vascular disease now count for an additional point each. This new metric, called CHA_2DS_2-VASc[10], can take on a value from 0 to 9 with higher scores indicating greater risk. The metric was developed after the WATCHMAN clinical program began and was not used prospectively to screen patients.

2.3   Warfarin Therapy as Standard of Care

The current standard of care for stroke prevention in patients with AF is long-term warfarin therapy. Long-term warfarin has been extensively studied both for its therapeutic benefit and long-term sequelae, and has demonstrated efficacy as well as significant complications affecting lifestyle and long-term care.

There is a wealth of published literature from controlled studies on stroke prevention in AF. The Stroke Prevention in Atrial Fibrillation (SPAF) studies examined treatment strategies for patients with non-valvular AF and provided evidence that forms the backbone of today's standard stroke prevention modalities. SPAF I showed a reduction in stroke events of 67% at one year, confirming that antithrombotic therapy with aspirin or warfarin was effective in ischemic stroke prevention. SPAF III confirmed that if the risk of thromboembolism justified antithrombotic therapy, warfarin adjusted for a target INR of 2.0 to 3.0 was most effective.[11,12]

Warfarin as a clinical treatment is not without its risks. The frequency of major bleeding or intracranial hemorrhage while on warfarin is high and must be weighed against the benefit of treatment for AF-related ischemic stroke and disability. Although chronic warfarin therapy has

been proven to reduce the risk of clinical thromboembolism among those with non-valvular AF, there are several difficulties in administering it, and discontinuation rates are high.[13,14] The use of warfarin requires routine lab monitoring to achieve an international normalized ratio (INR) of 2.0 – 3.0. Maintaining the INR within this narrow therapeutic range can be challenging. Frequent blood tests to monitor INR are required at some cost and inconvenience to the patient. In addition, because warfarin is affected by a large number of drug and dietary interactions; it can be unpredictable and difficult to manage. Chronic anticoagulation presents problems of safety and tolerability in many patients, especially those older than 75, the age group encompassing perhaps half of AF-associated strokes.[15] Approximately 40-50% of patients who should be treated with anticoagulation are not receiving it.[14]

2.4   Recent Oral Anticoagulant Therapy

After approval of the PREVAIL study protocol, three alternative oral anticoagulants became commercially available. A summary of these anticoagulants is provided below for discussion of alternatives to warfarin therapy. These drugs include: dabigatran (Pradaxa)[16], rivaroxaban (Xarelto)[17] and apixaban (Eliquis)[18].

2.4.1   Dabigatran (Pradaxa)

Dabigatran is a relatively new oral direct thrombin inhibitor approved by the FDA in October 2010 for prevention of stroke in patients with non-valvular atrial fibrillation. Dabigatran offers similar efficacy compared to warfarin therapy without frequent blood tests for INR monitoring. Unlike warfarin, however, there is no antidote to reverse the anticoagulant effect in the event of a major bleeding event. There is no reliable blood test to monitor the effects of dabigatran, making it difficult to verify therapeutic exposure.

In the RE-LY randomized clinical study, dabigatran administered at a dose of 150 mg BID, dabigatran was associated with lower rates (1.11%/year; P<0.001 for superiority) of stroke and systemic embolism but similar rates of major hemorrhage (3.11%/year) when compared to warfarin therapy (3.36%/year). The rate of hemorrhagic stroke was higher (0.38%/year) in the warfarin group as compared to 150 mg BID (0.10%/year; P<0.001) of dabigatran[16].

While dabigatran demonstrated efficacy, it is not without risks. The most common side effect of dabigatran was bleeding which was observed in more than one in ten patients. When compared to warfarin, patients taking dabigatran had fewer life threatening bleeds and fewer minor and major bleeds, including intracranial bleeds, but the rate of gastrointestinal bleeding was higher, mostly in patients >75 years. Concomitant drug use can also increase the risk of additional side effects. The use of antiplatelet agents increases the risk of major bleeds with dabigatran approximately two-fold. Concomitant use of antidepressants also showed an increase in bleeding risk, as well as increased risk of myocardial infarctions with the use of direct thrombin inhibitors. Similar to warfarin therapy, certain populations are contraindicated to dabigatran due to increased risk of side effects and discontinuation rates of the drug are high. Thus, 21% of

patients taking dabigatran at its recommended dose opted to discontinue therapy within 2 years, a discontinuation rate higher than that observed for warfarin.

2.4.2 Rivaroxaban (Xarelto)

Rivaroxaban (Xarelto) is a direct Factor Xa inhibitor approved by the FDA in July 2011 for prophylaxis of deep vein thrombosis (DVT) which can lead to pulmonary embolism (PE). In November 2011, the FDA approved the drug for stroke prophylaxis in patients with nonvalvular atrial fibrillation.

Unlike warfarin, dosage adjustments and routine coagulation monitoring are not required with rivaroxaban. However, there is no anecdote to specifically reverse the anticoagulant effect of rivaroxaban in the event of a major bleeding event.

In the ROCKET-AF randomized study comparing rivaroxaban with adjusted dose warfarin, the primary analysis revealed rivaroxaban (1.7%/year; P<0.001) was not inferior to warfarin (2.2%/year) in the prevention of subsequent stroke or systemic embolism. There were no significant differences in rates of major and clinically relevant non-major bleeding between the rivaroxaban (14.9%/year; P=0.44) and warfarin (14.5%/year), with significant reductions in intracranial hemorrhage (0.5% vs. 0.7%) and fatal bleeding (0.2% vs. 0.5%) in the rivaroxaban group. Bleeding from GI sites, including upper, lower, and rectal sites, occurred more frequently in the rivaroxaban group, as did bleeding that led to a drop in hemoglobin or bleeding that required transfusion. Additionally, 14.3% of patients discontinued their treatment medication by one year.[17]

A Risk Evaluation And Mitigation Strategy (REMS) has been instituted by FDA in conjunction with the manufacturer (Janssen Pharmaceuticals) out of recognition of an increased risk of thrombotic events if Xarelto is prematurely discontinued without introducing an adequate alternative anticoagulant, and potential decreased efficacy of Xarelto (15 mg and 20 mg) if not taken with the evening meal.

2.4.3 Apixaban (Eliquis)

Apixaban (Eliquis) is a direct Factor Xa inhibitor approved by the FDA in December 2012 for reducing the risk of stroke and dangerous blood clots (systemic embolism) in patients with nonvalvular atrial fibrillation.

The randomized clinical study ARISTOTLE comparing apixaban to warfarin therapy demonstrated apixaban was not inferior to warfarin therapy for the primary outcome of all stroke and systemic embolism (1.27%/year and 1.60%/year, respectively; p<0.001 for non-inferiority; p=0.01 for superiority). Major bleeding risk also favored apixaban over warfarin therapy (2.13%/year vs. 3.09%/year; P<0.001). The rate of hemorrhagic stroke was 0.24%/year in the apixaban group compared to 0.47%/year in the warfarin group (P<0.001). As with the other newer anticoagulants, the patient discontinuation rate of the treatment drug was high, about 25% by the end of the study.[18]

2.4.4 Summary

Meta-analyses of the reported treatment benefits of the newer anticoagulants, including dabigatran, rivaroxaban and apixaban, compared to warfarin therapy are few and vary depending on the anticoagulation control achieved by the warfarin cohorts. The data reported in contemporary clinical studies for these anticoagulants suggests all three agents are at least as efficacious as dose-adjusted warfarin, with similar major bleeding profiles. Adverse effects of the new anticoagulants compared to warfarin were lower for fatal bleeding and hemorrhagic stroke and numerically lower for major bleeding. However, they are not without their risks. Bleeding risks with any anticoagulant remain high and the newer anticoagulants do not have antidotes to reverse anticoagulation rapidly, in contrast to warfarin therapy. Bleeding risk may be increased for persons greater than 75 years of age or those on concomitant antiplatelet therapy. In addition, there remains a high rate of drug discontinuation.

2.5 LAA Closure Techniques

Removal of the left atrial appendage (LAA) to prevent stroke was first described during mitral valvulotomy procedures for rheumatic mitral stenosis in the 1930's.[19] More recent studies suggest that the left atrial appendage is the major source of thromboemboli in the context of AF. As a result, non-pharmacological approaches have been developed to mechanically close the LAA.[8,20,21,22,23] Procedures to obliterate or excise the LAA are routinely performed surgically with suture or staples, as an adjunct during open chest surgery or during minimally invasive procedures.

2.5.1 Surgical Closure

Surgical ligation of the LAA with suture has shown to be feasible, and has been performed during cardiac surgery, especially mitral valve surgery. In several investigations it was reported that surgical closure of the LAA may not completely seal the LAA from the LA circulation. One study in particular showed that incomplete surgical LAA closure was common, as investigators found evidence of patent flow into the LAA during follow-up evaluation by transesophageal echocardiogram (TEE) in a significant proportion of patients. In that study, 18 of 50 (36%) patients had incomplete LAA closure on subsequent TEE follow-up. Furthermore, spontaneous echo contrast or thrombus was detected within the appendages of 9 of 18 (50%) patients with incomplete closure. Most importantly, 4 of 18 (22%) patients had some type of thromboembolic event after the procedure indicating that the residual communication between the incompletely ligated LAA and the LA body might be a potential source of the increased embolic events.[24]

Stapling the LAA with a device during open chest surgery has been another approach to close the LAA. The LAAOS study compared a stapling device to suture ligation during coronary artery bypass grafting (CABG) in 77 patients. Using the surgical stapler, 24 of 33 (72%) patients demonstrated complete occlusion while only 5 of 11 (45%) patients using sutures had a similar result. Appendage tears were reported in 9 of 77 (12%) patients during LAA stapling surgery, and all were repaired with sutures. In the experience of those surgeons who performed at least 4

cases with the stapling device, the rate of complete LAA occlusion increased from 9 of 21 (43%) to 20 of 23 (87%) over that period.[25] A learning curve may play a role in achieving greater success rates with this stapler method.

2.5.2 *Percutaneous Closure*

Percutaneous closure of the LAA has been studied in human clinical studies since August 2001. Over time, the procedure has become more widely attempted and accepted as the design of LAA closure devices has improved and the implantation techniques and imaging methods have been refined. In addition, the understanding of the complex nature of the anatomy of the LAA has increased.

The PLAATO device was the first percutaneous LAA closure device implanted in humans. Two multi-center feasibility studies with the PLAATO device were conducted, one in Europe and one in North America from August 2001 until November 2003. The primary population included patients with non-rheumatic AF at high risk for ischemic stroke who were not candidates for long-term warfarin therapy. The primary study endpoint was the occurrence of major adverse events (new major or minor stroke, cardiac or neurologic death, myocardial infarction or the requirement for cardiovascular surgery) related to the PLAATO procedure within one month of the index procedure. The implant attempt was successful in 97.3% of patients. The annual stroke rate reported after an average of 9.8 months of follow-up was 2.2% in the 108 patients who underwent successful occlusion of the LAA.[26] After completing feasibility studies, the PLAATO device clinical study program stalled due to lack of funding, and a pivotal investigation of the device was never initiated.

The WATCHMAN LAA Closure Device was first implanted in humans in August 2002. Atritech (purchased by Boston Scientific in March 2011) successfully completed a feasibility (PILOT) study conducted in both Europe and the US, a randomized pivotal study (PROTECT AF) to assess safety and long-term efficacy of the WATCHMAN device, a non-randomized registry (CAP Registry) of 566 patients, PREVAIL, a second randomized study to gather supplemental data on the WATCHMAN device and its associated continue access registry (CAP2), and a European feasibility study of patients with contraindications to warfarin therapy (ASAP). Additional details on these studies and long-term effects of permanent implantation with the WATCHMAN device are included in Appendix A: Summary of WATCHMAN Studies.

Two additional device manufacturers have developed percutaneous left atrial appendage closure devices, including the Amplatzer™ Cardiac Plug/Amulet (St. Jude Medical) and WaveCrest™ (Coherex). Neither device has been approved in the U.S., although both devices have CE mark in the EU.

3 Treatment Group Descriptions

3.1 Investigational Device – WATCHMAN LAAC Therapy

3.1.1 Investigational Device Description

The WATCHMAN device is designed to be permanently implanted at, or slightly distal to, the ostium (opening) of the left atrial appendage (LAA) to prevent embolism of blood clots formed within the LAA. The placement procedure can be performed under general or conscious sedation in a catheterization or electrophysiology (EP) laboratory setting using standard transseptal technique under fluoroscopic and echocardiographic guidance.

The WATCHMAN LAAC Therapy is a three-component system, the WATCHMAN LAA Closure Device (WATCHMAN device), the WATCHMAN Delivery System and the WATCHMAN Access Sheath.

The implanted component of WATCHMAN is a novel device designed to prevent the embolism of thrombi that may form in the left atrial appendage. The WATCHMAN device may prevent the occurrence of ischemic stroke and systemic thromboembolism in patients with non-valvular atrial fibrillation (AF) who require treatment for potential thrombus formation and are eligible for warfarin therapy. It may also reduce the risk of life-threatening bleeding events such as hemorrhagic stroke as seen in patients on warfarin therapy but for whom the risks posed by long-term warfarin therapy outweigh the benefits. WATCHMAN is manufactured by Boston Scientific Corporation, received CE Mark in October 2005 and is under IDE in the U.S. Over 4000 commercial cases have been completed since commercial launch in 2009, and over 2000 patients have participated in clinical studies with the WATCHMAN device.

3.1.2 Proposed Indication for Use

The WATCHMAN LAAC Therapy is intended to prevent embolism of thrombus from the left atrial appendage and thus reduce the risk of stroke, systemic embolism, and cardiovascular death in high-risk patients with non-valvular atrial fibrillation who are eligible for warfarin therapy but for whom the risks posed by long-term warfarin therapy outweigh the benefits.

3.1.3 Components of the Investigational Device

3.1.3.1 WATCHMAN Device

The WATCHMAN device is comprised of a self-expanding nitinol frame structure with fixation anchors around the device perimeter and a permeable polyester fabric that covers the atrial facing surface of the device as shown in Figure 9. The device is constrained within the Delivery System until deployment into the LAA.

The WATCHMAN device is available in various sizes to accommodate a range of LAA ostial diameters. The device size, measured in mm, is the diameter of the device at its maximum dimension in an uncompressed (fully expanded) state. An appropriate device size is selected based on LAA measurements obtained utilizing fluoroscopy and transesophageal echocardiography (TEE).

Figure 9: WATCHMAN Device
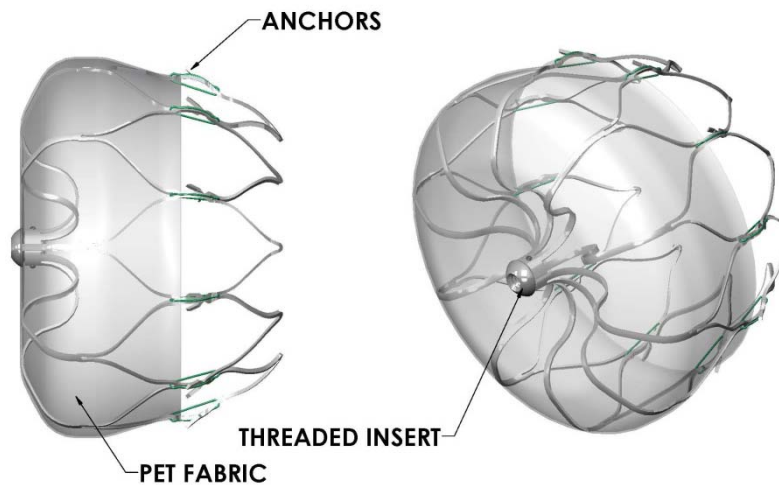
3.1.3.2 Delivery System

The delivery catheter consists of an inner core wire with a reinforced braided jacket that is connected to the deployment knob at the proximal end and a screw thread assembly at the distal end (Figure 10).

The WATCHMAN device is pre-loaded and is deployed by loosening the valve on the Delivery System and retracting the outer sheath. The WATCHMAN device can be partially recaptured and redeployed if the device is too distal. If the device is deployed too proximal, it can be fully recaptured prior to release from the threaded insert. Following a full recapture, the device cannot be redeployed and must be withdrawn from the delivery system and replaced with a new device. The device is released by rotating the device deployment knob counter clockwise.

Figure 10: WATCHMAN Delivery System
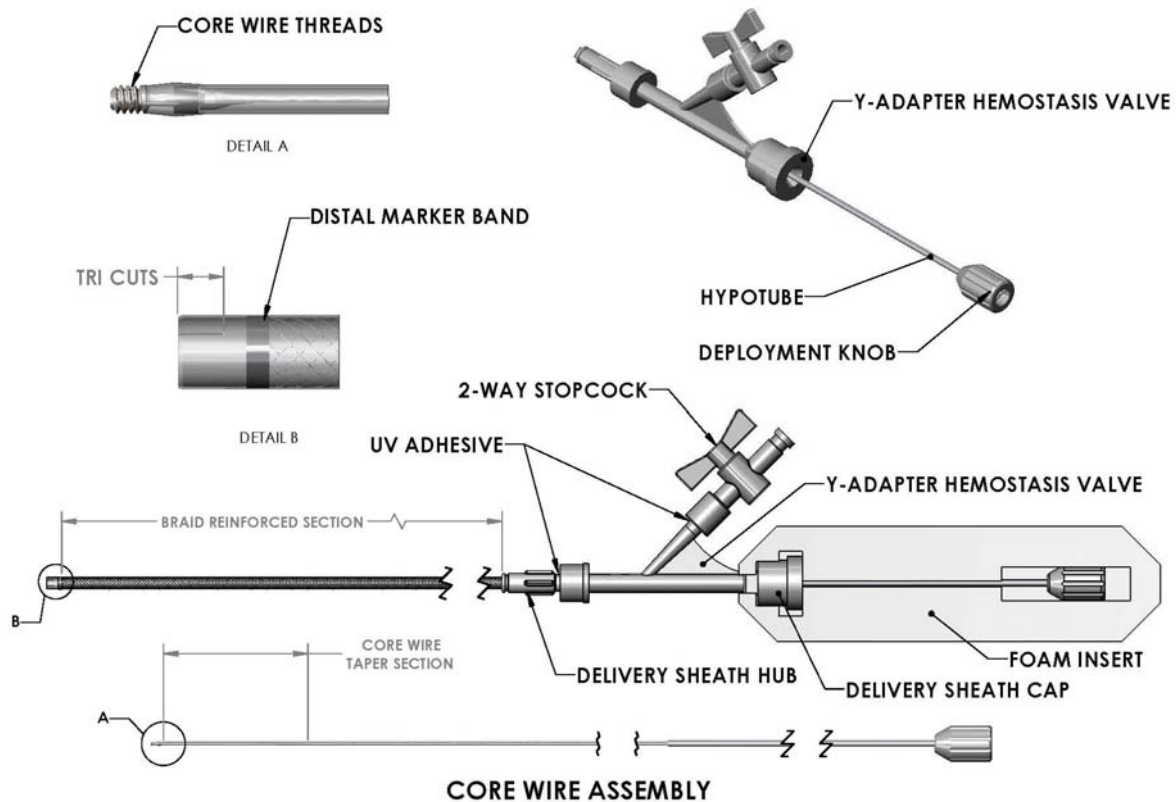
3.1.3.3 Access Sheath

The 14F (12F inner diameter (ID)) transseptal Access Sheath is utilized to gain access to the LAA and serves as a conduit for the Delivery System (Figure 11). The distal end of the Access Sheath is available in various curve styles to assist with placement of the sheath into the LAA. The distal tip contains a radiopaque marker band for in situ, fluoroscopic visualization as well as sizing marker bands used to gauge if the Access Sheath is positioned at the appropriate depth in the LAA based on the device size selected.

The Access Sheath and dilator are utilized to gain access to the LAA after initial transseptal access into the left atrium has been established. Once the Access Sheath is positioned into the left atrium and the dilator has been removed, it then serves as a conduit for the Delivery System. The Delivery System is introduced into the Access Sheath and the components snap together to act as one during device implantation.

Figure 11: WATCHMAN Access System
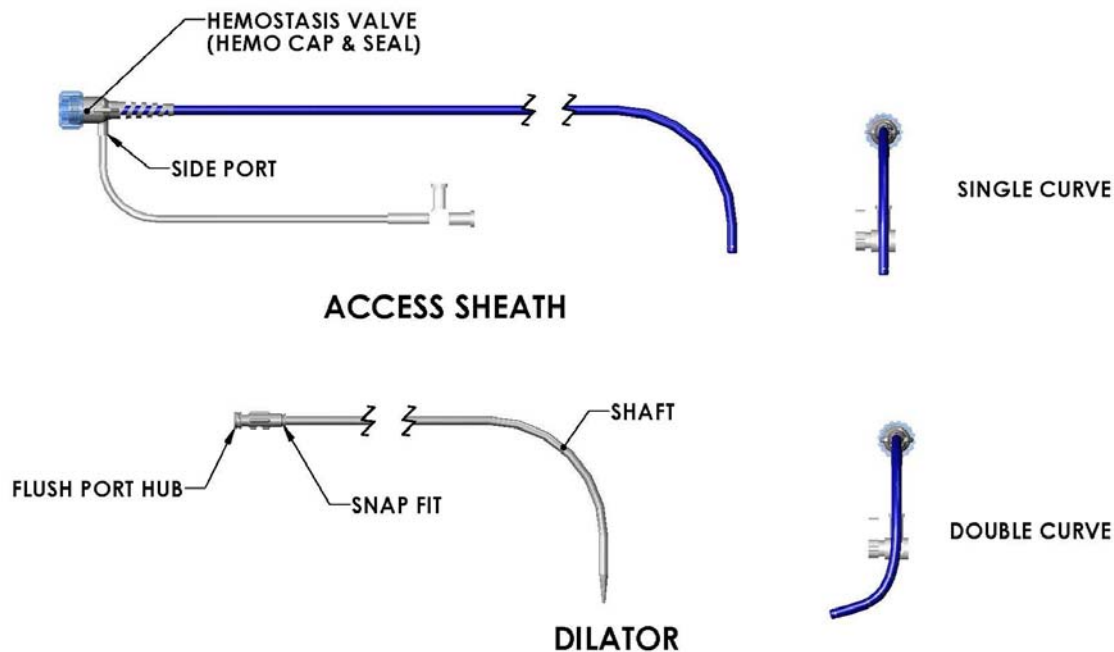
A copy of the proposed Directions for Use is located in Appendix B: Directions for Use.

3.2 Control Therapy Description - Warfarin or Warfarin Derivative

Anticoagulation with warfarin therapy is the accepted standard of care for patients with an increased risk for thrombosis, specifically patients with AF and other risk factors that increase the chance of stroke. Therefore, warfarin was selected as the treatment of choice for the Control Group of the two randomized studies. In the studies, all patients were required to be eligible to receive warfarin at the time of enrollment. Patients were also required to agree to remain on warfarin for the duration of the study if they were randomized to the Control Group of the study (i.e., long-term warfarin therapy.) The use of warfarin was mandated in the studies at actively participating centers; however, a variety of generic and trade name formulations were used, particularly in Europe (specifically Germany). The dosing requirements of warfarin derivatives can vary widely. In order to optimize the therapy, the anticoagulation level for patients in the Control Group was measured against the universally accepted therapeutic INR rather than a specific warfarin dose. All patients regardless of the anticoagulation therapy prescribed were monitored through frequent blood tests with the goal of maintaining a therapeutic INR of 2.0-3.0.[4] At the time of study enrollment, a baseline INR was required for each patient. Furthermore, Control patients were required to have their INR monitored during study participation. An INR monitoring worksheet was to be completed for all patients to record and provide this information to the investigator, and for data collection purposes to ensure monitoring against the therapeutic

INR level was consistent across centers. As monitoring of the INR was the method to confirm effective Control Group anticoagulation rather than mandating a specific warfarin derivative or dose, the opportunity for variations in patient outcomes in the Control Group was minimized.

4   History of WATCHMAN LAAC Therapy Clinical Trial Program

There are currently eight clinical trials either completed or underway to evaluate the WATCHMAN LAAC Therapy for the non-surgical closure of the left atrial appendage. Taken together, the results of these studies provide a reasonable assurance of the safety and efficacy of the WATCHMAN device and demonstrate a favorable benefit/risk profile. This program is comprised of two randomized controlled trials (PROTECT AF and PREVAIL), and two continued access registries (CAP and CAP2), and two feasibility studies (PILOT and ASAP).

The three studies and their contribution to supporting the safety and efficacy of the WATCHMAN device are described briefly in Table 11.

Table 11: Clinical Studies in WATCHMAN Program Used to Support Safety and Efficacy in Panel Pack

Study Name	Study Type	Description
PROTECT AF	Randomized	First randomized study
CAP	Continued Access	Continued Access for PROTECT AF
PREVAIL	Randomized	Second randomized study

Five additional studies round out the WATCHMAN clinical program as seen in Table 12. Results from these studies are not used in this panel pack since these studies are either ongoing, studied versions of the WATCHMAN device not under consideration for approval, or studied a patient population other than that for which approval is sought.

Table 12: Clinical Studies in WATCHMAN Program Not Used in Panel Pack

Study Name	Study Type	Description
PILOT	Feasibility	Feasibility trial of the WATCHMAN device
CAP2	Continued Access	Continued access for PREVAIL (this trial is currently enrolling)
ASAP	Feasibility	New patient population (patients contraindicated for warfarin)
EWOLUTION	Post-market	Post-market registry in Europe (this trial is currently enrolling)
WASP	Post-market	Post-market registry in Asia/Pacific (this trial is currently in its start-up phase)

The two randomized studies will be discussed in greater detail in Section 5. This section will provide a high-level overview of the other two feasibility and two continued access studies in the WATCHMAN program. A more detailed description of these studies and their results may be found in Appendix A: Summary of WATCHMAN Studies.

4.1.1   PILOT

The PILOT feasibility study was a prospective, non-randomized feasibility study of the WATCHMAN LAAC Therapy in the treatment of patients with non-valvular atrial fibrillation (AF) who required treatment for potential thrombus formation, were eligible for warfarin therapy, and had a CHADS$_2$ score of $\geq$ 1. This study met its safety and performance goals and allowed progression of the WATCHMAN program to randomized clinical trials. This study is not used in the report to support safety and efficacy due to its small size.

4.1.2   ASAP

The ASAP feasibility study was a prospective, non-randomized feasibility study designed to evaluate the WATCHMAN LAAC Therapy in the treatment of patients with non-valvular AF who required treatment for potential thrombus formation, were <u>contraindicated</u> to warfarin therapy, and had a CHADS$_2$ score of $\geq$ 1. Patients were prescribed aspirin and clopidogrel therapy post implant rather than the standard six week warfarin therapy regimen. The patients tended to be at a higher risk for stroke and bleeding and were older than patients in other LAAC trials. Similar follow-up was conducted, and the study demonstrated that the WATCHMAN device could be implanted safely in this patient population. Stroke rates seen in this study population had a stroke rate comparable to that observed in the PROTECT AF population despite the higher risk in these patients. This study is not used in the report to support safety and efficacy because it was evaluated in a different population.

4.2   Continued Access Registries

4.2.1   Continued Access to PROTECT AF (CAP)

The CAP Registry was a multicenter prospective non-randomized continued access registry supplementing the PROTECT AF study in the treatment of patients with non-valvular AF who required treatment for potential thrombus formation, were eligible for warfarin therapy, and had a CHADS$_2$ score of $\geq$ 1. This registry allowed continued access to patients following the PROTECT AF study.

This registry used the same composite endpoint (ischemic and hemorrhagic stroke, systemic embolism, and death from cardiovascular and unexplained causes) as PROTECT AF and PREVAIL. This study provided a significant reduction in procedure-induced stroke and an

increase in procedural success, coupled with a decrease in serious procedure-related complications when compared to PROTECT AF.

4.2.2 Continued Access to PREVAIL (CAP2)

The CAP2 Registry is a prospective, non-randomized, multicenter study following the PREVAIL randomized trial and is designed to evaluate the WATCHMAN Left Atrial Appendage Closure Therapy in the treatment of patients with non-valvular atrial fibrillation who required treatment for potential thrombus formation, were eligible for warfarin therapy, and had a $CHADS_2$ score of > 2 (or had a $CHADS_2$ score of = 1 if additional conditions/comorbidities are present).

A current cohort of 450, up to a maximum of 1500, WATCHMAN patients will be enrolled at up to 60 sites in the United States. Enrollment started September 25, 2012, and enrollment is ongoing. No data from this study will be presented to the committee since this study is still enrolling patients.

4.3 Post-Market Registries

The WATCHMAN Closure Device has received the CE Mark and is market-released outside the United States. EWOLUTION and WASP are prospective, non-randomized, multicenter studies and are intended to compile real-world clinical outcomes data in patients who are implanted with the WATCHMAN device in a commercial clinical setting and to collect real-world usage data that may be needed for reimbursement of WATCHMAN technology.

EWOLUTION is being conducted in Europe and will enroll a maximum of 1000 patients at up to 75 sites will be enrolled with follow-up extending to two years. WASP is being conducted in the Asia/Pacific region and will enroll a maximum of 300 patients at up to 10 sites with two-year follow-up.

5   Design Considerations for the PROTECT AF and PREVAIL Trials

5.1   Overview

The PROTECT AF and PREVAIL clinical studies were large, prospective studies conducted primarily in the United States; the PROTECT AF study also recruited patients in Europe. These two studies were randomized controlled trials of high risk individuals with non-valvular AF who were either were implanted with a WATCHMAN device and/or were randomized to a control group of patients who received warfarin.

The PROTECT AF study met its efficacy primary endpoint. The results were reviewed by a Circulatory System Devices Panel in April 2009, and the WATCHMAN device was voted as "Approvable with Conditions" by a 7-5 vote.

A second randomized study (PREVAIL) was undertaken to gather information to corroborate that the WATCHMAN Closure Device could be implanted safely and to show that new operators could be trained to implant the device safely. Additional outcomes of interest in PREVAIL included characterization of the specific mechanism of action of the WATCHMAN Closure Device and the study of patients at a higher risk of stroke.

5.2   Study Endpoints

5.2.1   Efficacy Primary Endpoint – PROTECT AF and PREVAIL

It was hypothesized that the risk of thromboembolic events due to thrombi escaping from the LAA could be reduced with the placement of a barrier between the LAA and the rest of the body. The WATCHMAN LAAC Therapy was designed for this role and successful deployment of the device could then result in permanent cessation of warfarin. To demonstrate the efficacy of the WATCHMAN device, an efficacy primary endpoint was used that consisted of a composite of stroke (ischemic and hemorrhagic), systemic embolism, and deaths due to cardiovascular or unexplained causes. This composite endpoint captured events that could be attributed to device use (ischemic stroke and systemic embolism), events possibly attributed to warfarin use (hemorrhagic stroke), and mortal events possibly related to the device or procedure (cardiovascular and unexplained deaths). This endpoint compared event rates between a cohort of patients implanted with the WATCHMAN device and a cohort of patients taking warfarin and was analyzed using Bayesian methods.

The PREVAIL study was designed to use prior information from the PROTECT AF study. Since the entry criteria were tightened in PREVAIL, only data from those patients in PROTECT AF who would have qualified for PREVAIL were used and given a weight of 50%.

5.2.2 Mechanism of Action Primary Endpoint - PREVAIL

A second primary endpoint was introduced for the PREVAIL study intended to evaluate only those components of the primary endpoint that were specific to the WATCHMAN device's mechanism of action, namely, ischemic stroke and systemic embolism. Events were counted starting at seven days post-procedure for patients in the Device cohort or seven days post-randomization for those patients randomized to the Control cohort.

5.2.3 Safety Endpoints – PROTECT AF and PREVAIL

The primary safety endpoint in PROTECT AF was treatment of patients without the occurrence of life-threatening events as determined by the Clinical Events Committee, which included events such as device embolization requiring retrieval, bleeding events such as pericardial effusion requiring drainage, cranial bleeding events due to any source, gastrointestinal bleeds requiring transfusion and any bleeding related to the device or procedure that necessitates an operation. This endpoint looked at safety events in both the device and control arms of the study.

The primary safety endpoint for PREVAIL differed from the primary safety endpoint used in PROTECT AF. The primary safety endpoint was defined as the occurrence of specific events[*] from the time of randomization to within 7 days of the procedure (Device arm) or discharge (Control arm). This endpoint was intended to better characterize the device- and procedure-related risks of the WATCHMAN device. This endpoint looked at safety events only in the device arm of the study and compared the event rates to an objective performance criterion (OPC).

5.2.4 Other Changes Incorporated into PREVAIL

To assess the training program, there were enrollment threshold set for both new sites and new operators. Results with new sites and new operators could then be stratified to evaluate the efficacy of the training regimen.

To help ensure that all patients enrolled were eligible for warfarin, additional conditions were placed such that patients with a $CHADS_2$ score of 1 had to have conditions or comorbidities that placed them at greater risk.

5.2.5 Summary

The endpoints used to evaluate PROTECT AF as well as the additional endpoint data from PREVAIL, when taken together, should provide a reasonable assurance of safety and efficacy of

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[*] All-cause death, ischemic stroke, systemic embolism, or device or procedure related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair. Percutaneous catheter drainage of pericardial effusions, snaring of an embolized device, thrombin injection to treat femoral pseudoaneurysm, and non-surgical treatments of access site complications were excluded from this endpoint.

the WATCHMAN device. For simplicity, this panel pack will use the following nomenclature to describe the endpoints of the PREVAIL study:

- Efficacy Primary Endpoint: The endpoint that describes the composite of events *(first primary endpoint)*.

- Mechanism of Action Primary Endpoint: The endpoint that focuses only on ischemic stroke and systemic embolism beyond the seven-day post randomization period *(second primary endpoint)*.

- Safety Primary Endpoint: The endpoint that characterizes the peri-procedural risk *(third primary endpoint)*.

6 Investigational Plan

This section provides a high-level overview of the investigational plans for the PROTECT AF and PREVAIL studies and the CAP Registry

6.1 Patient Eligibility

The major entry criteria will be discussed in this section. A full list of entry criteria are listed in Appendix C: Entrance Criteria.

The major inclusion criteria were identical for PROTECT AF and the CAP Registry and nearly identical for PREVAIL. Eligible patients for both randomized studies were those ≥18 years old with documented paroxysmal, persistent, or permanent non-valvular atrial fibrillation (i.e., the patient has not been diagnosed with rheumatic mitral valvular heart disease), eligible for long-term warfarin therapy, and eligible to come off warfarin therapy if the LAA is sealed (i.e., the patient has no other conditions that would require long-term warfarin therapy suggested by current standard medical practice).

Major exclusion criteria excluded patients that had a mechanical valve, a need for long-term warfarin, a contraindication to warfarin, or evidence from a transesophageal echo (TEE) that indicated thrombus in the LAA, poor anatomy, atheroma, mitral valve stenosis, or tumor. Other exclusion criteria included symptomatic carotid disease, a left ventricular ejection fraction < 30%, presence of an atrial septal defect, atrial septal repair, or closure device, or an ablation planned within 30 days.

The major entry criterion that differed between the two studies was the $CHADS_2$ score, which defined the stroke risk as well as the eligibility for warfarin. In PROTECT AF, patients with a $CHADS_2$ score of 1 or greater were eligible. In PREVAIL, patients with a $CHADS_2$ score =1 could qualify if additional risk stratifiers were present. These conditions include any one of the following:

- Female aged 75 or older

- Baseline LVEF ≥ 30 and < 35%

- Age 65-74 and had diabetes or coronary artery disease

- Age 65 or greater and had congestive heart failure

Adding these criteria to PREVAIL helped to ensure that patients were eligible for warfarin therapy and also helped to define a higher risk patient population. Patients taking clopidogrel were also excluded from PREVAIL in order to mitigate FDA concerns surrounding effects that can be attributed to concomitant medical therapy.

6.2 Screening

All three studies employed similar screening techniques. Those patients who provided informed consent and met all the Inclusion and Clinical Exclusion Criteria underwent echocardiographic examination (TTE and TEE) to further evaluate Echocardiographic Exclusion Criteria. Baseline screening included a medical and cardiac history, current medical status, vital signs and AF status, a pregnancy test (for women of child-bearing potential), laboratory analysis (hemoglobin, platelet count, serum creatinine) and a current medication regimen including the use of antiplatelet, antiarrhythmic, NSAID, and anticoagulation medications.

Active assessments included a neurologic assessment by a Neurologist, and assessment of quality of life using instruments specifically for stroke patients (NIH Stroke Scale, Barthel Index, and Modified Rankin Scale).

Finally, echocardiographic assessments were performed. A transthoracic echo (TTE) was performed unless one was completed in the prior 30 days and the patient did not have an appreciable difference in cardiac status since the TTE was performed. A transesophageal echo (TEE) was required to be completed prior to randomization to confirm eligibility criteria.

6.3 Roll in Patients (PROTECT AF and PREVAIL Only)

The two randomized studies permitted the use of roll-in patients to allow investigators to become familiar with the device and its implant prior to randomizing patients while the CAP Registry did not.

Roll-in patients followed the same procedures and follow-up schedule as patients randomized to the device; however, their data was analyzed separately from randomized patients and their experience did not contribute to the primary endpoint analysis.

6.4 Randomization Methods (PROTECT AF and PREVAIL Only)

After the Roll-in cohort was enrolled at a site, subsequent patients who qualified for the study were randomized in a 2:1 allocation to receive the WATCHMAN device or control (2 device patients to 1 control patient). The CAP Registry was a single-arm observation study in which all patients were to undergo an implant procedure of the WATCHMAN device.

6.5 Device Group

6.5.1 Implant Procedure Overview

The implant procedure was performed percutaneously under conscious sedation or general anesthesia in either a cardiac catheterization or electrophysiology laboratory setting. The device was a permanent implant positioned distal to the ostium of the LAA using a standard transseptal technique.

Conventional transseptal catheterization was performed using angiography and/or echocardiography. Hand injections of contrast medium were performed in multiple views to provide LAA angiograms and assist with catheter manipulation.

Since the LAA is a complex structure, TEE with fluoroscopy was utilized to accurately size the LAA orifice diameter and length in numerous angles. TEE was also used to assess the number and orientation of LAA lobes, the anatomic relationship between the pulmonary veins and criteria for device release including proper device positioning and flow around the device after implantation.

6.5.2 Post Procedure Medication Guideline

Implanted patients were to be on warfarin therapy through at least the 45-day follow-up TEE. Implanted patients were also prescribed 81mg aspirin per day while on warfarin therapy to mitigate platelet aggregation on the device during the healing process[2].

Patients in the Device Group who were successfully implanted with a device underwent a TEE to assess device performance at 45 days, 6 months and 12 months. Evaluations of residual flow into the LAA, device stability, device position, residual atrial septal shunt and intracardiac thrombus were made during the echocardiographic examinations in accordance with the Imaging Protocol.

Patients in the Device Group remained on warfarin until a TEE evaluation demonstrated adequate seal of the LAA. Therefore, the earliest possible visit in which device patients could discontinue warfarin therapy was the 45-day visit. Per the protocol, subjects randomized to the Device group were to discontinue warfarin therapy when the TEE indicates there is complete seal around the perimeter of the WATCHMAN device or a residual jet flow of ≤ 5 mm around the margins of the device. If the 45-day TEE showed adequate seal of the LAA, warfarin was discontinued, and clopidogrel and aspirin were prescribed until the 6-month visit. If the 45-day TEE did not show sealing of the LAA, the patient was to remain on warfarin therapy and aspirin until the 6-month TEE was performed to assess LAA seal. Refer to Figure 12 for the medication guidelines for Device patients.

After the 6-month visit and evidence of successful LAA seal, device patients discontinued clopidogrel/warfarin and remained on aspirin at a recommended daily dose of 325 mg indefinitely.

Figure 12: Medication Guidelines for Device Patients


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                    ┌─────────────────────────────────────┐
                    │         Implant – 45 day             │
                    │ Warfarin: dosage to achieve INR 2.0-3.0 │
                    │  Aspirin: 81 mg while on warfarin    │
                    │        Clopidogrel: No               │
                    └─────────────────────────────────────┘
                          /                        \
       LAA Seal per 45 Day TEE            NO LAA Seal per 45 Day TEE
                        /                            \
    ┌──────────────────────────┐         ┌──────────────────────────┐
    │    45 day – 6 Months     │         │    45 day – 6 Months     │
    │     Warfarin: No         │         │     Warfarin: Yes        │
    │   Aspirin: 325 mg*       │         │ Aspirin: 81 mg while on warfarin │
    │    Clopidogrel: Yes      │         │     Clopidogrel: No      │
    └──────────────────────────┘         └──────────────────────────┘
                │                                    │
    ┌──────────────────────────┐    ┌────────────────────────────────────────┐
    │    6 Months – 5 Years    │    │          6 Months – 5 Years            │
    │     Warfarin: No         │    │ Warfarin: Discontinued when seal is adequate │
    │   Aspirin: 325 mg*       │    │              Aspirin:                  │
    │    Clopidogrel: No       │    │    On warfarin - 81 mg while           │
    └──────────────────────────┘    │  Off warfarin - 325 mg* indefinitely   │
                                     │          Clopidogrel: No               │
                                     └────────────────────────────────────────┘
*recommended dosage
```

Device patients were followed long term to re-assess their medical status and the occurrence of adverse events.

6.6   Control Group

Patients randomized to the control group were to remain on warfarin for the duration of the study. Dosage was adjusted such that patients maintain a therapeutic INR of 2.0 – 3.0.

A baseline INR was obtained for each patient at the time of study enrollment. Medical necessity for interruptions in warfarin therapy (such as cardiovascular and non-cardiovascular interventions, procedures, diagnostic testing, etc.) was documented on the Warfarin/INR eCRF. Documentation included the reason and dates of interruption. While patients were not required to have an INR during the time off warfarin, careful attention was given to ensure compliance to the INR monitoring requirement of every 28 days once warfarin was restarted.

The aforementioned Guideline indicates there is no added benefit or protection from thromboembolic events for patients on warfarin plus aspirin therapy. Treatment of control

patients with aspirin within the PREVAIL study was not recommended. If a control patient was on warfarin and aspirin therapy during the study, the rationale for this therapy combination was collected on the eCRF at subsequent follow-up visits.

Control patients were followed long-term to re-assess their medical status and the occurrence of adverse events.

6.7   Follow-Up

Enrolled patients in both groups were required to receive follow-up assessment of their medical status and to be evaluated for the occurrence of adverse events. Patients were followed at post-enrollment intervals of 45 days, 6 months, 9 months, 12 months, semi-annually through 5 years (PROTECT AF and CAP Registry), and semi-annually through 3 years and thereafter annually through 5 years (PREVAIL) or until study termination. Each follow-up visit and corresponding data including adverse events was documented on the appropriate eCRFs. A high level overview of the study design is depicted in Figure 13.

Figure 13: Study Design Overview
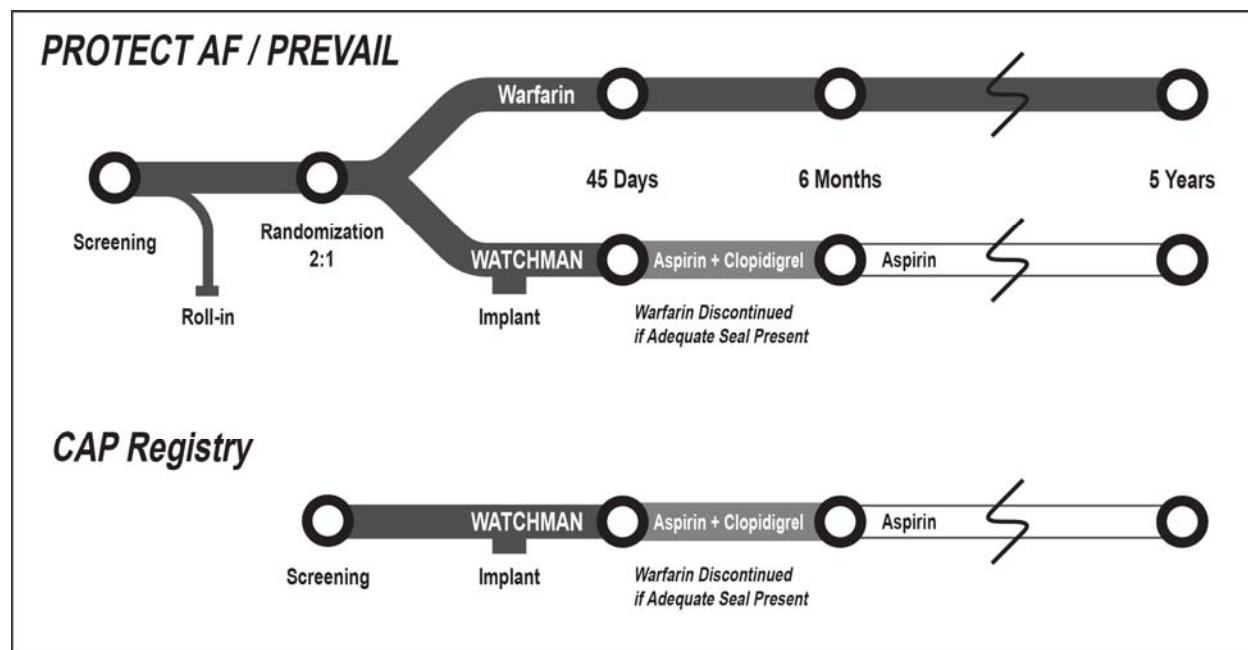
6.8 Summary Comparison of PROTECT AF and PREVAIL Studies

Table 13: Comparison of Key Elements of the PROTECT AF and PREVAIL Studies

Characteristic	PROTECT AF	PREVAIL
Study Design	Randomized controlled trial 2:1 randomization Device/Control	Same
Patients / Centers	800 patients 59 US and European centers	461 patients 41 US sites
Key Entry Criteria	Age ≥ 18 Documented non-valvular AF Eligible for long-term warfarin Eligible for warfarin cessation if LAA is sealed	Same
	Clopidogrel use permitted	Clopidogrel use excluded if within 7 days prior to implant
	CHADS$_2$ Score ≥ 1	CHADS$_2$ Score ≥ 2 CHADS$_2$ Score =1 with conditions[◊]
Efficacy Primary Endpoint	Composite of: • Ischemic stroke • Hemorrhagic stroke • Systemic embolism • Cardiovascular/unexplained death	Same
Mechanism of Action Primary Endpoint	Not applicable	Occurrence of ischemic stroke or systemic embolism > 7 days
Safety Primary Endpoint	Freedom from occurrence of life-threatening events as determined by the Clinical Events Committee[**]	Occurrence of specific events[*] within 7 days of the procedure or discharge
	Evaluated in both Device and Control Groups	Evaluated in Device Group only
Study Oversight	• Clinical Events Committee • Data and Safety Monitoring Board	Same

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[◊] Conditions include any one of the following: Female age 75 or older, has a baseline LVEF between 30-35%, is age 65-74 and had diabetes or coronary artery disease, or is age 65 or greater and has congestive heart failure

[**] Included events such as device embolization requiring retrieval, bleeding events such as pericardial effusion requiring drainage, cranial bleeding events due to any source, gastrointestinal bleeds requiring transfusion and any bleeding related to the device or procedure that necessitates an operation.

[*] All-cause death, ischemic stroke, systemic embolism, or device or procedure related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair. Percutaneous catheter drainage of pericardial effusions, snaring of an embolized device, thrombin injection to treat femoral pseudoaneurysm, and non-surgical treatments of access site complications were excluded from this endpoint.

7 Data Requirements and Study Management

The processes and procedures by which clinical data was collected, recorded and reported in the PROTECT AF and PREVAIL studies are briefly described in the following sections.

7.1 Adverse Event Handling

Adverse events were handled in accordance with the protocols and adjudicated by the Clinical Events Committee (CEC). For the full list of adverse event handling requirements, reference Appendix D: Adverse Event Handling Procedures and Appendix E: CEC Adverse Event Definitions.

7.2 Independent Committees

7.2.1 Clinical Event Committee

The PROTECT AF, CAP Registry, and PREVAIL studies employed independent Clinical Events Committees (CEC) to review and adjudicate site-reported adverse events and ascertain their seriousness, relationship of the event to the device or procedure, and relationship of study medications to the study endpoints.

Each study CEC was comprised of two interventional cardiologists and one neurologist. Additionally, the PREVAIL CEC had a second Neurologist and Interventional Neuroradiologist participate during any meeting in which a potential stroke, TIA, or systemic embolism event was to be reviewed. The Chairperson was the same for the PROTECT AF and PREVAIL studies. Table 14 and Table 15 list the CEC members and their affiliation.

Table 14 PROTECT AF and CAP Registry Clinical Events Committee Members

Member	Specialty / Affiliation
Brian Lew, MD, FACC *Chairperson*	Interventional Cardiology Minnesota Heart Clinic Minneapolis, MN
Dominic Plucinksi, MD	Interventional Cardiology Minnesota Heart Clinic Minneapolis, MN
Eve Rogers, MD	Neurology Reynoldsburg, OH

Table 15: PREVAIL Clinical Events Committee Members

Member	Specialty / Affiliation
Brian Lew, MD, FACC *Chairperson*	Interventional Cardiology Minnesota Heart Clinic Minneapolis, MN
Michael Manoles, MD, FACC	Interventional Cardiology Minnesota Heart Clinic Minneapolis, MN
Robert Taylor, MD	Vascular and Interventional Neurology University of Minnesota Medical Center Minneapolis, MN
Additional Members for Neurologic Event Review	
Alejandro Rabinstein, MD	Vascular Neurology Mayo Clinic Rochester, MN
Charles Truwit, MD	Interventional Neuroradiology Hennepin County Medical Center Minneapolis, MN

No member of the CEC was directly involved in the conduct of the study. No member had financial, proprietary, professional, or other interests that could affect impartial decision-making, other than compensation for their time and participation on the committee.

7.2.2 *Data Safety Monitoring Board*

An independent Data and Safety Monitoring Board (DSMB) was established for the review of data and safety parameters in the PROTECT AF, CAP Registry, and PREVAIL studies.

Members of the DSMB included two interventional cardiologists, an electrophysiologist, and a biostatistician. No member of the DSMB was directly involved in the conduct of the study. No

member had financial, proprietary, professional, or other interests that could affect impartial decision-making, other than compensation for their time and participation on the committee.

7.3 Data Quality Assurance

Boston Scientific Corporation was responsible for study monitoring, data management, and statistical analyses for this study.

Clinical sites were monitored at regular intervals during the study to ensure that all aspects of the currently approved protocol were followed. The investigator and study site personnel ensured that designated BSC personnel and Regulatory Authorities had access to source documents as appropriate.

A Clinical Quality Assurance (CQA) audit program was developed and implemented by Clinical Quality Assurance, an independent quality assurance team at BSC. Clinical investigators and vendors approved by BSC were audited by CQA at periodic intervals to assess continued compliance to required standards.

7.4 Single Site Violation of Good Clinical Practice

On November 1, 2011, Boston Scientific (BSC) was notified by the Principal Investigator (PI) at an investigational site participating in the WATCHMAN clinical studies (PROTECT AF, CAP Registry and PREVAIL) of a potential data integrity issue associated with the WATCHMAN studies conducted at his site. BSC communicated with FDA on this single site violation of Good Clinical Practice verbally on November 10, 2011, via email on November 16, 2011 and December 5, 2011, and via IDE supplement on December 6, 2011 (IDE/S094) and April 16, 2012 (IDE/S099).

BSC included the data from this site that was substantiated through independent source records. Data that could not be independently verified was censored and not included in the final data sets. A complete discussion of the background and a sensitivity analysis of the data are located in Appendix F: Single Center Violation of Good Clinical Practice and Sensitivity Analysis.

8   Statistical Methods

8.1   General Statistical Methods

The primary pre-specified analysis of both PROTECT AF and PREVAIL was defined as intent-to-treat in the sense that all patients were analyzed according to their randomized assignment irrespective of the treatment actually received. All available data were used in both Bayesian analyses, primarily expressed as rates of events over time.

Patient-years were calculated from the date of randomization to the first appropriate event or censoring date (for patients without an event) for each patient and aggregated over analysis groups. Patients who exited the study had an End of Study case report form completed which was the indicated censoring date for those patients without an event.

Methods of survival analysis (i.e., the Kaplan-Meier approach) were used to analyze all available data. These methods have the advantage of using the maximal amount of information for patients that have not yet experienced an event. Where the methods of survival analysis were not appropriate, all available data are included for analysis

Descriptive statistics were generated for the data collected at baseline, during the procedure and at follow-up. For continuous variables, the mean, standard deviation, and range were reported.

8.2   Statistical Design - PROTECT AF

The statistical objective for the efficacy primary endpoint was to determine if the Device Group was non-inferior to the Control Group with respect to the event rate for the composite efficacy primary endpoint. Event rate was defined as the expected number of events per 100 patient years of follow-up. A Bayesian model stratified on $CHADS_2$ score was used for evaluation of the statistical objective. Sequential evaluation of the statistical objective allowed for early stopping for futility or non-inferiority if the study data gave clear indications for the decision.

8.2.1   Sequential Analysis Plan

The first sequential interim analysis was performed after collection of 600 patient years of follow-up, which included 300 patients with one year of follow-up and 100 patients with two years of follow-up. Subsequent analyses are allowed after each additional 150 patient years up to a maximum of 1500 patient years of follow-up. At each interim analysis, posterior distributions for the event rates for the Device Group and the Control Group were calculated and the following criteria were assessed in order.

8.2.2 Criterion for Non-inferiority

The criterion for establishing non-inferiority at an interim analysis was a posterior probability that the event rate for the Device Group was less than 2 times the event rate for the Control Group of at least 0.975 and that the preceding criterion for futility was not met.

8.2.3 Criterion for Superiority

The criterion for establishing superiority was a posterior probability that the event rate for the Device Group was less than the event rate for the Control Group of at least 0.95. The superiority test was only performed if non-inferiority had been established.

If neither "Futility" nor "Non-inferiority" (nor "Superiority") were declared, the decision for the interim analysis was "Undecided," and an additional 150 patient years of follow-up was to be collected before the next evaluation time, up to a limit of 1500 patient years of follow-up. If after the maximum of 1500 patient years of follow-up the Device Group was not established as "Non-inferior", the device was to be considered "Not Non-inferior."

8.3 Statistical Design – PREVAIL

There were two efficacy endpoints: the efficacy primary endpoint and the mechanism of action primary endpoint. The statistical objective for each was to determine if the WATCHMAN device was non-inferior to the control group with respect to the 18-month event rate for each of the primary endpoints. With the first two endpoints, a Bayesian adaptive design was used to select the sample size and uses historical priors from the previous pivotal study with the device, the PROTECT AF study.

The primary safety endpoint was only analyzed for patients randomized to the device arm, and a statistical comparison for the composite was made against a performance goal. The third endpoint was not incorporated into the Bayesian adaptive design where early stopping for success is based on a comparison of the randomized groups for the efficacy and mechanism of action primary endpoints. However, because of the seriousness and acute nature of this third endpoint, a safety/futility stopping guideline was used.

8.4 Statistical Design – CAP Registry

The CAP Registry followed the PROTECT AF study and used the same entry criteria and the same efficacy and safety endpoint and events underwent review by the CEC. It was a single-armed observational study and, consequently, there were no hypothesis tests associated with the endpoints. Study results were to be summarized with descriptive statistics rather than with analytical statistics.

8.5   Sample Size

8.5.1   PROTECT AF

The design parameters of the sequential analysis plan were chosen to provide adequate probability of success (analogous to frequentist "power") in situations where the device is truly non-inferior and to ensure an acceptable false-positive rate (analogous to frequentist "Type I" error rate) in situations where the device is not non-inferior. These parameters provide for acceptable operating characteristics across a range of Device and Control Group event rates.

The historical basis for event rates was derived from the SPAF studies database, which is a compilation of data from three clinical trials concerning the effects of warfarin and aspirin for patients with AF. In cooperation with Carl van Walraven, M.D., event rates for the composite event of all stroke, cardiovascular death or systemic embolism were computed for patients assigned to receive full dose warfarin among clinical trials included in the SPAF database. This data was used to provide rates for evaluation of the Sequential Bayesian Analysis Plan in determining the sample size.

Forming a weighted average of the event rates for the different $CHADS_2$ scores, the overall event rate was expected to be 6.15 events per 100 patient years. This rate formed the basis for the sample size for the PROTECT AF study.

8.5.2   PREVAIL

An adaptive design with a flexible sample size was used. The sample size ranged from a minimum of 300 patients to a maximum of 400 randomized patients. Due to a single center violation in GCP, 407 patients were randomized (see Section 7.4).

Interim analyses for the purpose of determining the final sample size were permitted when 300 patients were enrolled and then again every 25 patients, until a sample size stopping rule was reached or the maximum sample size of 400 was reached. At these sample size interim analyses the predictive probabilities for study success at the current sample size was calculated. When enrollment accrual ceased, all patients were to be followed for 6 months before the final analysis could occur.

8.6   Statistical Methods – PROTECT AF

All patients not having an event or lost to follow-up were censored at the time of the last documented follow-up visit or last known status. Patient years was calculated for each patient from the date of randomization to the appropriate event or censoring date (for patients without an event) and aggregated over analysis groups. Event rates were calculated as the number of events per 100 patient years of follow-up.

8.6.1 Primary Analysis Dataset (Pre-specified)

The primary analysis cohort consisted of all randomized patients, analyzed according to their randomly assigned treatment group. Event status and censoring was determined regardless of the treatment actually received.

8.6.2 Secondary Analysis Dataset: Post Procedure (Pre-specified)

While the primary efficacy analysis cohort includes all randomized patients in the group to which they were assigned, other analyses may be performed to exclude certain enrolled patients that were not able to benefit from the treatment. One such analysis is a post procedure analysis to examine the long-term treatment effect following implant of the device. Understanding that any catheter intervention has its inherent risks, from a clinician perspective it is important to answer the following questions: 1) What happens once the procedure is complete? and 2) Are there any adverse events that the clinician needs to be aware of to educate the patient before leaving the hospital?

8.6.3 Secondary Analysis Dataset: Per-Protocol (Pre-specified)

In the PROTECT AF study, one potential bias was the possible time lag between the implantation of the device and the time at which warfarin therapy could be discontinued. During this time, the patients were exposed to both the risks of the implantation procedure and the risks of warfarin therapy, without the potential benefit of being off warfarin. Important questions from the patient perspective are: 1) Will I be able to stop warfarin and if so, what are the chances? and 2) What are the outcomes after being taken off warfarin therapy?

To quantify the potential benefit of the device, a per-protocol analysis was performed that only included randomized Device patients who were successfully implanted with the device that were then able to discontinue warfarin therapy and only included Control patients that were taking warfarin therapy at baseline or 45-days.

8.7 Statistical Methods – PREVAIL

8.7.1 Efficacy Primary Endpoint

The efficacy primary endpoint was the composite endpoint of hemorrhagic stroke, ischemic stroke, systemic embolism, and cardiovascular or unexplained death.

The WATCHMAN device demonstrated non-inferiority to the Control Group if the upper bound of the equitailed 2-sided 95% credible interval for the 18-month risk ratio of the first primary endpoint was less than 1.75.

A piecewise exponential model was used to model the 18-month event rates. The hazards were modeled for the following intervals: 0-7 days, 7-60 days, 60-182 days, and 182+ days. Event rates were assumed to be constant within the 4 separate intervals but could vary across intervals.

Event rates were estimated separately for the Device and Control Group and event types (cardiovascular/unexplained death + hemorrhagic stroke vs. ischemic stroke + systemic embolism).

8.7.2   Mechanism of Action Primary Endpoint

The mechanism of action primary endpoint was the composite endpoint of ischemic stroke and systemic embolism occurring greater than 7 days after randomization.

The WATCHMAN device demonstrated non-inferiority to the Control Group if the upper bound of the equitailed 2-sided 95% credible interval for the 18-month risk ratio of the endpoint was less than 2.0 <u>or</u> the upper bound of the equitailed 2-sided 95% credible interval for the 18-month risk difference of the endpoint was less than 0.0275 (18-month rates for the second endpoint excluded events occurring in the first 7 days after randomization).

A piecewise exponential model was used for both outcomes to model time varying hazards (e.g. the risk of systemic embolism or ischemic stroke may be higher in the device group immediately after procedure then decrease thereafter). The hazards were modeled for the following intervals: 0-7 days, 7-60 days, 60-182 days, and 182+ days.

8.7.3   Analysis of the Primary Endpoints for Efficacy and Mechanism of Action

For the first and second primary endpoints, the model for hazard rate is noted in **Equation 1**

Equation 1 - First and Second Primary Endpoints Hazard Rate Model

$$\lambda_{G,Z}(t) = \begin{cases} \lambda_{G,Z,1} & 0 < t \le 7 \\ \lambda_{G,Z,2} & 7 < t \le 60 \\ \lambda_{G,Z,3} & 60 < t \le 182 \\ \lambda_{G,Z,4} & 182 < t \end{cases}$$

where t was measured in days, $G \in \{D,C\}$ where D represented the Device Group and C represented the Control Group, and $Z \in \{1,2\}$ where Z=1 for cardiovascular/unexplained death and hemorrhagic stroke and *Z*=2 for ischemic stroke and systemic embolism and the index of 1 – 4 denotes the piecewise intervals.

The probability of no event within a time period *T* of length *t* was exp($-\lambda_{G,Z,T}t$). Therefore the probability of an event for the primary analysis within 18 months for group G is noted in Equation 2

Equation 2 – Probability of Any Event by 18 Months

$$r_{G,A} = \text{Pr}(\text{Any Event by 18 months in Group } G) =$$
$$1 - \exp\left(-\left(7\left(\lambda_{G,1,1} + \lambda_{G,2,1}\right) + 53\left(\lambda_{G,1,2} + \lambda_{G,2,2}\right) + 122\left(\lambda_{G,1,3} + \lambda_{G,2,3}\right) + 365\left(\lambda_{G,1,4} + \lambda_{G,2,4}\right)\right)\right)$$

The probability of a second endpoint event within 18 months (excluding the first 7 days) for group G is noted in Equation 3.

Equation 3 – Probability of Thrombolic Event by 18 Months

$$r_{G,T} = \text{Pr}(\text{Thrombolic Event by 18 months in Group } G) =$$
$$1 - \exp\left(-\left(53\lambda_{G,2,2} + 122\lambda_{G,2,3} + 365\lambda_{G,2,4}\right)\right)$$

where $\lambda_{G,Z,T}$ was the rate in events per day.

Event rates were summed for the primary endpoint rate because exposure times were the same in both event types. This was mathematically equivalent to tracking time to first event where the event could be any of the four event types.

The posterior distributions were calculated separately for the event rates in each time period, treatment group, and event type. The posterior distribution for the 18-month event rates in both the device and control groups is then calculated.

8.7.3.1 Prior distributions

Historical priors for each interval in the piecewise exponential were based on data from the previous PROTECT AF study, specifically data from the 1588 patient-year data set (locked on April 14, 2010). Data from the PROTECT AF study was discounted 50%.

For each event rate, $\lambda_{G,Z,T}$, for group G, event type Z, and time period T, we assume a prior of the form

$$\lambda_{G,Z,T} \sim \Gamma(\alpha_{G,Z,T}, \beta_{G,T}).$$

where $\alpha_{G,Z,T}$ = one-half the events of type Z observed in time period T in group G from the PROTECT AF study and $\beta_{G,T}$ = one-half the exposure time in days observed in time period T in group G from the PROTECT AF study. If there were no events, the value of $\alpha_{G,Z,T} = 0.001$ was substituted for 0 to ensure a proper posterior distribution.

Table 16 reports the prior parameters for each value group, segment, and endpoint.

Table 16: PROTECT AF: Events and Exposure by Treatment and Event Type

| Group | Event Type | Time Period | PROTECT AF | | Prior | |
			Observed Events	Exposure (days)	α	B
Control	1	0-7	0	1368	0.001	684
	1	7-60	1	10154	0.5	5077
	1	61-182	3	22742	1.5	11371
	1	183+	12	129037	6	64518.5
	2	0-7	0	1368	0.001	684
	2	7-60	1	10154	0.5	5077
	2	61-182	0	22742	0.001	11371
	2	183+	7	129037	3.5	64518.5
Device	1	0-7	0	2422	0.001	1211
	1	7-60	1	17603	0.5	8801.5
	1	61-182	1	37953	0.5	18976.5
	1	183+	8	230799	4	115399.5
	2	0-7	7	2422	3.5	1211
	2	7-60	1	17603	0.5	8801.5
	2	61-182	3	37953	1.5	18976.5
	2	183+	8	230799	4	115399.5

Event type 1= cardiovascular/unknown death or hemorrhagic stroke
Event type 2=ischemic stroke or systemic embolism

8.7.3.2 Posterior Distributions

After observing $Ev_{G,Z,T}$ total events of type Z in group G within period T and with total patient exposure time $Expos_{G,T}$ in group G within period T the posteriors are identified in Equation 4.

Equation 4 – Posterior Distribution for $\lambda_{G,Z,T}$

$$\left[\lambda_{G,Z,T} \mid Ev_{G,Z,T}, Expos_{G,T} \right] \sim \mathrm{Gamma}\left(\alpha_{G,Z,T} + Ev_{G,Z,T}, \beta_{G,Z,T} + Expos_{G,Z} \right)$$

When an event was observed, patients were considered censored to any future events, including events of the "other" type. Therefore, exposure time does not have an event type subscript. Exposure time was always equal within treatment group and time period for the two event types.

The posterior distributions were calculated for the event rates $\lambda_{G,Z,T}$ for each event type (Z=1,2), treatment group (G=D,C) and time period (T=1,2,3,4) according to Equation 4. This was done using Monte Carlo simulation with conjugate priors.

Given the posterior distributions for each group, the posterior distribution was calculated for the primary endpoint, the 18-month event rates, $r_{D,A}$ and $r_{C,A}$, for the Device and Control Groups according to Equation 2 and the posterior distribution for the risk ratio $rr_A = r_{D,A} / r_{C,A}$.

If the upper bound of the equitailed 95% credible interval for rr_A was less than 1.75 then the 18-month event rate for the composite endpoint in the Device Group was considered non-inferior to Control (warfarin). Stated as a null and alternative hypothesis:

$$H_o: rr_A \geq 1.75$$
$$H_a: rr_A < 1.75$$

Using the posteriors for Equation 4 for the second endpoint rates, the posterior distribution for the 18-month event rates for the second endpoint occurring greater than seven days post randomization, $r_{D,T}$ and $r_{C,T}$ for the Device and Control Groups were calculated according to equation (3). The posterior distributions for the risk ratio $rr_T = r_{D,T} / r_{C,T}$ and risk difference, $rd_T = r_{D,T} - r_{C,T}$ were calculated. If the upper bound of the equitailed 95% credible interval for $rr_T < 2.0$ or if the upper bound of the equitailed 95% credible interval for the $rd_T < 0.0275$, then the 18-month event rate for the second endpoint in the Device Group was considered non-inferior to Control (warfarin). Stated as a null and alternative hypothesis:

$$H_o: rr_T \geq 2.0 \text{ and } rd_T \geq 0.0275$$
$$H_a: rr_T < 2.0 \text{ or } rd_T < 0.0275$$

8.7.4 *Final Analyses of the PREVAIL Efficacy Endpoints*

The final analyses were to be performed 6 months after the last patient was enrolled. The posterior distributions for the event rates $\lambda_{G,Z,T}$ were calculated for each event type (Z=1,2), treatment group (G=D,C) and time period (T=1,2,3,4) according to Equation 4.

The posterior distribution for 18-month event rates was calculated for any event, rG,A, for the Device and Control Groups according to equation (2) and the posterior distribution for the risk ratio $rrA = rD,A / rC,A$.

If the upper bound of the equitailed 95% credible interval for rrA was less than 1.75 then the 18-month event rate for the composite endpoint in the Device Group was considered non-inferior to the Control Group.

The posterior distribution for the 18-month event rates for thrombolic events sans the first seven days, rG,T, for the device and control groups were calculated according to equation (3). The posterior distributions for the risk ratio $rrT = rD,T / rC,T$ and risk difference, $rdT = rD,T - rC,T$ were calculated. If the upper bound of the equitailed 95% credible interval for $rrT < 2.0$ or if the upper bound of the equitailed 95% credible interval for the $rdT < 0.0275$, then the 18-month event rate for the thrombolic endpoint in the Device Group was considered non-inferior to the Control Group.

8.7.5   Safety Primary Endpoint

The primary safety endpoint was defined as the occurrence of one of the following events between the time of randomization and within 7 days of the procedure or by hospital discharge, whichever is later: all-cause death, ischemic stroke, systemic embolism, or device or procedure related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair. Percutaneous catheter drainage of pericardial effusions, snaring of an embolized device, thrombin injection to treat femoral pseudoaneurysm and non-surgical treatments of access site complications were excluded from this endpoint. This endpoint was analyzed only for patients randomized to the Device Group, and statistical comparison for the composite was made against a performance goal.

Success for this endpoint was achieved if the percentage of patients (p_o) experiencing one of these events was statistically less than the performance goal (PG) with at least 95% posterior probability, or equivalently if the 1-sided 95% credible interval was less than the performance goal. Stated as a null and alternative hypothesis:

$$H_o: p_o \geq PG$$
$$H_a: p_o < PG$$

A performance goal of 2.67% was proposed with a posterior probability criterion of 0.95. Success for this endpoint was achieved if the posterior probability of the percentage of patients with events was less than the performance goal exceeds 95%, or equivalently if the upper bound for the one-sided 95% credible interval was less than the performance goal.

Based on the components described in the SAP, a conservative performance goal of 2.67% was proposed for the evaluation of this endpoint. Given this value of 2.67%, this endpoint was considered successful if at most 4 of 200 or 6 of 267 device patients experienced the endpoint. These values were within the range of event rates supported by literature.

9 Results

9.1 Enrollment and Demographics

9.1.1 Enrollment Accountability

In PROTECT AF, a total of 800 patients were enrolled at 59 sites in the United States and Europe from February 14, 2005 through June 30, 2008. Of these, 707 patients were randomized patients [463 WATCHMAN and 244 warfarin control] and 93 non-randomized patients were roll-in WATCHMAN patients.

In the PREVAIL study, a total of 461 patients (407 randomized patients [269 WATCHMAN and 138 warfarin control] and 54 WATCHMAN roll-in patients) were enrolled at 41 sites in the United States from November 1, 2010 through June 28, 2012. Patients continue to be followed through their 5 year follow-up visit at the time of this report.

A 2:1 randomization allocation ratio was implemented across investigational sites in the randomized cohort. In PROTECT AF, a total of 800 patients were enrolled at 59 sites in the United States and Europe from February 14, 2005 through June 30, 2008. Of these, 707 patients were randomized patients (463 WATCHMAN and 244 warfarin control) and 93 non-randomized patients were roll-in WATCHMAN patients. Figure 14 summarizes patient enrollment across treatment groups, including nonrandomized Roll-in patients for the PROTECT AF and PREVAIL randomized studies and the CAP Registry.

Figure 14: Patient Flow Diagram
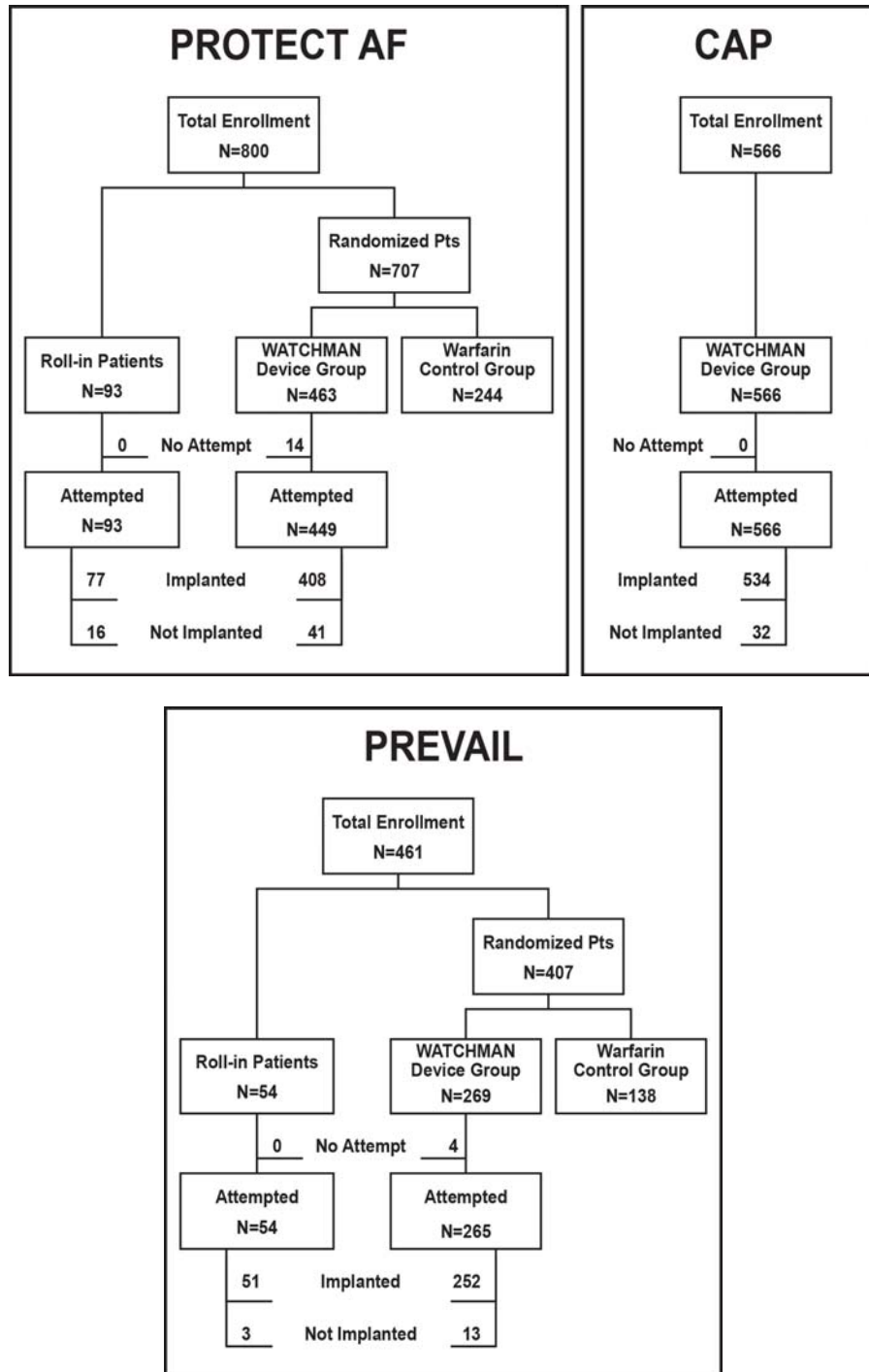
9.1.2 PREVAIL Enrollment in Grouped by New and Experienced Enrollment

The protocol required that a minimum of 20% of randomized patients be enrolled by new sites and at least 25% of randomized patients be enrolled by new operators. This latter requirement allowed for the inclusion of new operators at experienced sites. New site or operators were those with no prior participation in a WATCHMAN clinical study; i.e., the initial experience with WATCHMAN was within the PREVAIL study. Experienced sites and operators were those with participation in the prior PROTECT AF study.

Table 17 summarizes the percentage of patients enrolled by new and experienced operators and sites. The upper tier in this table describes enrollment based upon whether the site is new or experienced. The lower tier in this table delineates whether the operator is new or has previous experience.

Table 17: New and Experienced Enrollment – PREVAIL Study

Category	Device Group	Control Group	Randomized Total	Percentage Enrolled
New Site	104/269 (38.7%)	54/138 (39.1%)	158/407	38.8%
Experienced Site	165/269 (61.3%)	84/138 (60.9%)	249/407	61.2%
New Operator	105/269 (39.0%)	54/138 (39.1%)	159/407	39.1%
Experienced Operator	164/269 (61.0%)	84/138 (60.9%)	248/407	60.9%

New sites contributed to 38.8% (158/407) of randomized patients, thus meeting the protocol requirement of a minimum of 20% of enrolled patients. New operators enrolled 39.1% (159/407) patients achieving the protocol requirement of a minimum of 25% of enrolled patients.

9.1.3 Basic Demographics

Table 18 summarizes the randomized patient baseline demographic information.

Table 18: PROTECT AF, PREVAIL, and CAP Registry: Baseline Demographics

Characteristic	PROTECT AF		PREVAIL		CAP N=566
	Device N=463	Control N=244	Device N=269	Control N=138	
Age (years)	71.7 ± 8.8 (463) (46.0 ,95.0)	72.7 ± 9.2 (244) (41.0 ,95.0)	74.0 ± 7.4 (269) (50.0 ,94.0)	74.9 ± 7.2 (138) (53.0 ,90.0)	74.0 ± 8.3 (566) 44.0, 94.0
Height (inches)	68.2 ± 4.2 (462) (54.0 ,82.0)	68.4 ± 4.2 (244) (59.0 ,78.0)	68.4 ± 4.3 (269) (57.0 ,80.0)	68.5 ± 4.0 (138) (57.0 ,78.0)	68.2 ± 4.2 (566) 57.0, 79.0
Weight (lbs)	195.3 ± 44.4 (463) (85.0 ,376.0)	194.6 ± 43.1 (244) (105.0 ,312.0)	196.3 ± 44.9 (269) (106.0 ,333.0)	197.1 ± 43.3 (138) (112.0 ,317.0)	193.5 ± 45.2 (565) 91.0, 349.0
Gender					
Female	137/463 (29.6%)	73/244 (29.9%)	87/269 (32.3%)	35/138 (25.4%)	195/566 (34.5%)
Male	326/463 (70.4%)	171/244 (70.1%)	182/269 (67.7%)	103/138 (74.6%)	371/566 (65.5%)
LVEF (%)	57.3 ± 9.7 (460) (30.0, 82.0)	56.7 ± 10.1 (239) (30.0, 86.0)	55.4 ± 10.0 (268) (30.0, 80.0)	56.0 ± 9.8 (137) (30.0, 77.0)	---
Race/Ethnicity					
Asian	4/463 (0.9%)	1/244 (0.4%)	1/269 (0.4%)	1/138 (0.7%)	9/566 (1.6%)
Black/African American	6/463 (1.3%)	5/244 (2.2%)	6/269 (2.2%)	1/138 (0.7%)	11/566 (1.9%)
Caucasian	425/463 (91.8%)	222/244 (94.1%)	253/269 (94.1%)	131/138 (94.9%)	520/566 (91.9%)
Hispanic/Latino	25/463 (5.4%)	15/244 (2.2%)	6/269 (2.2%)	5/138 (3.6%)	20/566 (3.5%)
Native American/Alaskan	1/463 (0.2%)	1/244 (0.4%)	1/269 (0.4%)	0/138 (0.0%)	---
Other	2/463 (0.4%)	0/244 (0.7%)	2/269 (0.7%)	0/138 (0.0%)	6/566 (1.1%)

Continuous variables are presented in each cell as Mean ± SD and (N) (Min, Max)

Categorical variables are presented in each cell as n/N (%)

There were no statistically significant differences between the Device and Control Groups within each study. Baseline demographics demonstrate that patients in the two treatment groups within each study were comparable. All patients with atrial fibrillation who presented to the participating investigator were to be screened and randomized based on their characteristics and willingness to participate regardless of their gender or race.

9.1.3.1 CHADS$_2$ Score

The CHADS$_2$ score is a metric used to define the risk of stroke in a given patient. The score ranges from 0 to 6 and included weighted components using clinical measures shown to be correlated to stroke risk. Larger values indicate a greater the risk of stroke. This metric has typically been used in clinical practice to determine whether a patient should receive antiplatelet or anticoagulant therapy.[9]

To calculate a patient's CHADS$_2$ score, one point was assigned each for the presence of congestive heart failure, history of hypertension, age 75 years or older, and diabetes, and two points assigned for prior stroke or TIA. In PROTECT AF, a CHADS$_2$ score of ≥ 1 was necessary. In PREVAIL, the entry criterion for the CHADS$_2$ score was raised to 2 and but permitted with a CHADS$_2$ score of 1 to be enrolled if they met any of the following criteria:

- Patient was a female age 75 or older
- Patient had a baseline LVEF $\geq 30\%$ and $< 35\%$
- Patient was age 65-74 and had diabetes or coronary artery disease
- Patient was age 65 or greater and had documented congestive heart failure

The distribution of the CHADS$_2$ score and its components are shown in Table 19. There were no statistically significant difference in scores between the Device and Control Group within each study with the exception of hypertension in PREVAIL.

Calculating the mean CHADS$_2$ score using the value as a continuous variable resulted in a mean of 2.1±1.0 for the PROTECT AF study, a mean of 2.6±1.0 for the PREVAIL study and a mean of 2.5±1.2 for the CAP Registry. This increase was to be expected since the inclusion criteria for PREVAIL were designed to enroll a population at greater risk of stroke by requiring additional conditions placed on the participation of patients with CHADS$_2$ scores of 1.

Table 19: PROTECT AF, PREVAIL, and CAP Registry: CHADS$_2$ Score and Components

Risk	PROTECT AF		PREVAIL		CAP N=566
	Device N=463	Control N=244	Device N=269	Control N=138	
CHADS$_2$ Score (Categorical)					
1*	156/463 (33.7%)	66/244 (27.0%)	21/269 (7.8%)	12/138 (8.7%)	132/566 (23.3%)
2	158/463 (34.1%)	88/244 (36.1%)	137/269 (50.9%)	62/138 (44.9%)	200/566 (35.2%)
3	89/463 (19.2%)	51/244 (20.9%)	65/269 (24.2%)	36/138 (26.1%)	120/566 (21.2%)
4	37/463 (8.0%)	24/244 (9.8%)	33/269 (12.3%)	21/138 (15.2%)	78/566 (13.8%)
5	19/463 (4.1%)	10/244 (4.1%)	12/269 (4.5%)	7/138 (5.1%)	32/566 (5.7%)
6	4/463 (0.9%)	5/244 (2.0%)	1/269 (0.4%)	0/138 (0.0%)	4/566 (0.7%)
By Individual Component					
CHF	124/463 (26.8%)	66/244 (27.0%)	63/269 (23.4%)	32/138 (23.2%)	108/566 (19.1%)
History of Hypertension	415/463 (89.6%)	220/244 (90.2%)	238/269 (88.5%)	134/138 (97.1%)	502/565 (88.8%)
Age $\geq$ 75	190/463 (41.0%)	115/244 (47.1%)	140/269 (52.0%)	78/138 (56.5%)	293/566 (51.8%)
Diabetes	113/463 (24.4%)	72/244 (29.5%)	91/269 (33.8%)	41/138 (29.7%)	141/566 (24.9%)
Previous TIA/Ischemic Stroke	82/463 (17.7%)	49/244 (20.1%)	74/269 (27.5%)	39/138 (28.3%)	172/566 (30.4%)

9.1.3.2 CHA$_2$DS$_2$-VASc Risk Stratification

The CHADS$_2$ score has undergone refinement to produce the CHA$_2$DS$_2$ VASc risk stratification scoring system that includes additional risk factors for stroke and adds additional weight to age. This score was calculated by assigning one point each for congestive heart failure, hypertension, diabetes, vascular disease, age 65- 74, female sex, and 2 points of age $\geq$ 75 and 2 points for a previous stroke or TIA.[10] The range of values possible with this metric is 0-9 and is similar to the CHADS$_2$ score in that higher values are associated with greater risk of stroke. It is best for differentiating patients at low risk of stroke. With this instrument, a score of 0 corresponds to low risk, a score of 1 corresponds to moderate risk and a score of 2 or greater corresponds to high risk.

There was no predefined enrollment criterion based on CHA$_2$DS$_2$-VASc as the scoring system was developed after the initiation of the PREVAIL study. The distribution by CHA$_2$DS$_2$-VASc

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* The CHADS$_2$ score was higher in PREVAIL due to the additional risk stratifiers required for patients with a CHADS$_2$ score = 1.

score for the PROTECT AF and PREVAIL studies is shown in Table 20. This result indicates the success of the PREVAIL study design in recruiting high risk patients since 100% of PREVAIL patients were classified as high risk (CHA_2DS_2-VASc ≥ 2) using this metric vs. 91.1% of patients in PROTECT AF.

Table 20: Distribution of CHA_2DS_2-VASc Score at Baseline

Risk (Categorical)		PROTECT AF (n=707)	PREVAIL (n=407)	CAP (n=564)
Low	0	2 (0.3%)	0	0
Moderate	1	60 (8.6%)	0	24 (4.3%)
High	2	159 (22.7%)	26 (6.4%)	80 (14.2%)
	3	203 (29.0%)	122 (30.0%)	163 (28.9%)
	4	138 (19.7%)	130 (31.9%)	143 (25.4%)
	5	77 (11.0%)	87 (21.4%)	88 (15.6%)
	6	46 (6.6%)	32 (7.9%)	46 (8.2%)
	7	10 (1.4%)	9 (2.2%)	17 (3.0%)
	8	4 (0.6%)	1 (0.2%)	1 (0.2%)
	9	0	0	1 (0.2%)
Risk (Continuous) Mean ± SD (Range)		3.3 ± 1.4 (0 ,8)	4.0 ± 1.2 (2 ,8)	3.7 ± 1.4 (1 ,9)

9.1.3.3 Atrial Fibrillation

Atrial fibrillation (AF) can be categorized by its temporal pattern per ACC/AHA/HRS guidelines as follows[4]:

- Paroxysmal (i.e., self-terminating or intermittent) AF — Recurrent AF (≥2 episodes) that terminates spontaneously in seven days or less, usually less than 24 hours.

- Persistent AF — AF that fails to self-terminate within seven days. Episodes often require pharmacologic or electrical cardioversion to restore sinus rhythm.

- Permanent AF — Permanent AF is a term used to identify individuals with persistent atrial fibrillation where a decision has been made to no longer pursue a rhythm control strategy

As shown in Table 21, the most common patterns in descending order were paroxysmal, permanent, and persistent AF for the PROTECT AF and PREVAIL studies. AF pattern was not available from the CAP Registry. There was no statistically significant difference in the distribution of AF pattern within each study.

Table 21: PROTECT AF, PREVAIL, and CAP Registry: Atrial Fibrillation Pattern

AF Pattern	PROTECT AF		PREVAIL		CAP Registry N=566
	Device N=463	Control N=244	Device N=269	Control N=138	
Paroxysmal	200 (43.2%)	99 (40.6%)	131 (48.7%)	71 (51.4%)	242 (42.8%)
Persistent	97 (21.0%)	50 (20.5%)	85 (31.6%)	39 (28.3%)	171 (30.2%)
Permanent	160 (34.6%)	93 (38.1%)	42 (15.6%)	22 (28.3%)	136 (24.0%)
Unknown/Paced	6 (1.3%)	2 (0.8%)	11 (4.1%)	6 (4.3%)	17 (3.0%)

9.1.3.4 Left Atrial Appendage

Anatomic characteristics of the LAA were obtained by means of an echocardiographic imaging protocol at all participating centers to measure LAA length and ostium measurements appropriately. There were no appreciable differences noted in the anatomical dimensions of the left atrial appendage measured at baseline between treatment groups. Both groups were similar in that the average length of the LAA was approximately 29 mm while the average ostium size was approximately 21 mm as measured during the baseline TEE. In both groups the majority of patients had one major LAA lobe. However, 45.1% of Device Group patients and 34.3% of Control Group patients had more than one LAA lobe.

Baseline LAA characteristics as measured by TEE were recorded and reported by the site for enrolled patients and are summarized in Table 22.

Table 22: PREVAIL Baseline LAA Characteristics

Characteristic	Device N=269	Control N=138	P-value
Number of LAA Lobes			0.037
More than one	120/266 (45.1%)	47/137 (34.3%)	
One	146/266 (54.9%)	90/137 (65.7%)	
Maximum LAA Length, mm	29.2 ± 5.7 (265) (17.3 ,48.0)	29.5 ± 6.9 (137) (16.3 ,55.0)	0.583
Maximum LAA Ostium Diameter, mm	21.4 ± 3.3 (266) (13.7 ,31.6)	21.7 ± 3.6 (137) (15.5 ,38.0)	0.399

Values presented are mean ± standard deviation, n (minimum, maximum) or number of patients/total number of patients (%) as appropriate. P-values are from two sample t-tests or chi-square tests as appropriate comparing the randomized groups.

9.1.4 Follow-up Visit Compliance

Table 23, Table 24, and Table 25 provide an accounting of follow-up visit attendance in the PROTECT AF and PREVAIL studies and the CAP Registry, respectively. Consistently high levels of compliance were attained throughout the studies.

Table 23: PROTECT AF Follow-up Visit Attendance

Visit	Device Group Attended/ Expected (%)	Control Group Attended/ Expected (%)	Roll-in Attended/ Expected (%)	Total Attended/ Expected (%)
45 Day	433/438 (98.9%)	236/240 (98.3%)	90/91 (98.9%)	759/769 (98.7%)
6 Month	400/402 (99.5%)	226/231 (97.8%)	83/83 (100.0%)	709/716 (99.0%)
9 Month	386/392 (98.5%)	216/223 (96.9%)	83/83 (100.0%)	685/698 (98.1%)
12 Month	379/386 (98.2%)	203/219 (92.7%)	80/80 (100.0%)	662/685 (96.6%)
18 Month	374/381 (98.2%)	198/214 (92.5%)	77/77 (100.0%)	649/672 (96.6%)
24 Month	351/369 (95.1%)	174/201 (86.6%)	76/77 (98.7%)	601/647 (92.9%)
30 Month	341/358 (95.3%)	169/192 (88.0%)	72/73 (98.6%)	582/623 (93.4%)
36 Month	320/349 (91.7%)	149/176 (84.7%)	67/73 (91.8%)	536/598 (89.6%)
42 Month	321/338 (95.0%)	143/165 (86.7%)	67/73 (91.8%)	531/576 (92.2%)
48 Month	319/332 (96.1%)	138/156 (88.5%)	64/70 (91.4%)	521/558 (93.4%)
54 Month	293/307 (95.4%)	120/138 (87.0%)	64/68 (94.1%)	477/513 (93.0%)
60 Month	204/226 (90.3%)	94/107 (87.9%)	62/66 (93.9%)	360/399 (90.2%)
Total:	4121/4278 (96.3%)	2066/2262 (91.3%)	885/914 (96.8%)	7072/7454 (94.9%)

Table 24: PREVAIL Follow-up Visit Attendance

Visit	Device Attended/ Expected (%)	Control Attended/ Expected (%)
45-Day	259/261 (99%)	132/137 (96%)
6-Month	239/241 (99%)	129/132 (98%)
9-Month	177/181 (98%)	89/93 (96%)
12-Month	142/144 (99%)	77/78 (99%)
18-Month	72/74 (97%)	39/39 (100%)
2 Years	9/9 (100%)	2/2 (100%)

Table 25: CAP Registry Follow-up Visit Attendance

Visit	Attended/Expected (%)
45 Day	561/562 (99.8%)
6 Month	507/522 (97.1%)
9 Month	501/515 (97.3%)
12 Month	490/508 (96.5%)
18 Month	482/494 (97.6%)
24 Month	458/480 (95.4%)
30 Month	339/354 (95.8%)
36 Month	186/198 (93.9%)
42 Month	71/77 (92.2%)
48 Month	5/7 (71.4%)
Total:	*3600/3717 (96.9%)*

9.1.5 Patient Status

The patient status for the PROTECT AF, CAP Registry, and PREVAIL studies are provided in Table 26 and are current as of the data lock. In PROTECT AF, 313 patients (67.6%) in the Device Group and 134 (54.9%) of the Control Group either completed the study or were still active as of the last data query. Death was the most common reason for not completing the study [44 patients (18.0%) in the Control Group and 56 patients (12.1%) in the Device Group]. Patients in the Control Group of PROTECT AF were more likely to withdraw consent (44 patients, 18.4%) than in the Device Group (15 patients, 3.2%).

In PREVAIL, 123 patients (89.1%) of the Control Group were still active compared to 233 patients (86.6%) in the Device Group. Attrition due to death occurred in 5 patients (3.6%) in the Control Group compared to 13 patients (4.8%) in the Device Group. As in PROTECT AF, patients in the Control Group were more likely to withdraw consent than patients in the Device Group [8 patients (5.8%) vs. 2 patients (0.7%), respectively).

In the CAP Registry, 456 (80.6%) patients were still active with 53 (9.4%) lost due to death and 10 patients (1.8%) who have withdrawn follow-up.

Table 26: PROTECT AF, CAP Registry, and PREVAIL: Patient Status

Status	PROTECT AF		PREVAIL		CAP Registry (N=566)
	Device (N=463)	Control (N=244)	Device (N=269)	Control (N=138)	
Completed Five Years	202 (43.6%)	92 (37.7%)	0	0	0
Active as of Data Lock	111 (24.0%)	42 (17.2%)	233 (86.6%)	123 (89.1%)	456 (80.6%)
Death	57 (12.3%)	44 (18.0%)	13 (4.8%)	5 (3.6%)	53 (9.4%)
Lost to Follow-up	13 (2.8%)	11 (4.5%)	2 (0.7%)	1 (0.7%)	10 (1.8%)
Patient Consent Withdrawn	17 (3.7%)	45 (18.4%)	2 (0.7%)	8 (5.8%)	10 (1.8%)
Other	12 (2.6%)	10 (4.1%)	2 (0.7%)	1 (0.7%)	5 (0.9%)
No Device Implanted	51 (11.0%)	N/A	17 (6.3%)	N/A	32 (5.7%)

9.2   Procedural Data

The procedural data contained in this section is an analysis of the data from the randomized groups in PROTECT AF and PREVAIL only and from the CAP Registry.

9.2.1   Implant Procedure

Implant Procedure Success was defined as the successful delivery and release of a WATCHMAN Device into the LAA. A successful implant occurred in 90.9% (408/449) of patients for whom an implant procedure was attempted in PROTECT AF. In the CAP registry, the implant success rate improved to 534/566 patients (94.3%). This high implant success rate was sustained in the PREVAIL study, with a successful implant occurring in 95.1% (252/265) of patients for whom an implant procedure was attempted.

Implant procedure time was calculated as the time from venous access to time of release of the final WATCHMAN device. The mean procedure time for successfully implanted patients was similar between the two randomized studies with a mean procedure time of 57.4 ± 30.4 minutes for PROTECT AF and a mean procedure time of 58.6 ± 26.6 minutes in PREVAIL.

9.2.2   Full Device Recaptures

During each implant procedure, device release criteria of position, compression, stability and seal were assessed. If one or more release criteria were deemed not acceptable, the device could undergo full or partial device recapture. Fully recaptured devices are those which were completely removed and replaced, as required by the protocol and instructions for use. The incidence of full device recaptures that occurred in the PROTECT AF and PREVAIL study is

presented in Table 27. Device recapture data were not available from the CAP Registry. These results indicate an improved ability to meet the criteria needed to release the WATCHMAN device.

Table 27: PROTECT AF and PREVAIL: Full Device Recaptures

Number of Full Recaptures	PROTECT AF	PREVAIL
	Device N/Total (%)	Device N/Total (%)
0	261/449 (58.1)	184/265 (69.4%)
1	108/449 (24.1)	48/265 (18.1%)
2	45/449 (10.0)	18/265 (6.8%)
3	18/449 (4.0)	10/265 (3.8%)
4+	17/449 (3.8)	5/265 (1.9%)

9.3   Study Medications

9.3.1   *Device Group Warfarin Cessation*

Device Group patients had their warfarin dosage adjusted post procedure to achieve a therapeutic INR of 2.0 – 3.0. They were to remain on warfarin until a TEE evaluation showed adequate seal of the device in the LAA ostium such that the jet around the perimeter of the device was ≤ 5mm. The earliest possible visit in which device patients could discontinue warfarin therapy was the 45-day visit. If the 45-day TEE did not show adequate seal of the LAA, the patient was to remain on dose-adjusted warfarin therapy and aspirin until the 6-month or 12-month TEE confirmed adequate seal.

Table 28 shows the warfarin cessation rate for the Device Group in the PROTECT AF and PREVAIL studies and for the CAP Registry.

Table 28: PROTECT AF Warfarin Cessation – Successfully Implanted Device Systems

Visit	PROTECT AF (N=408)	PREVAIL (N=252)	CAP (N=566)
	Device N/Total (%)	Device N/Total (%)	Device N/Total (%)
45 Day	348/401 (86.8%)	227/246 (92%)	507/529 (95.8%)
6 Month	355/385 (92.2%)	235/239 (98%)	493/500 (98.6%)
12 Month	345/370 (93.2%)	141/142 (99%)	455/472 (96.4%)

9.3.2 Control Group Time in Therapeutic Range

Time in Therapeutic Range (TTR) is the standard benchmark for assessment of effective anticoagulation. It is calculated using the Rosendaal method which incorporates the frequency and values of INR measurements over time. The target threshold for TTR is estimated between 58% and 65% and below this threshold there appears to be little benefit of anticoagulation therapy over antiplatelet therapy.

The TTRs in the WATCHMAN clinical trial program compare favorably to those observed in other contemporary randomized clinical trials. In PROTECT AF, it was calculated that patients remained in the therapeutic range (INR 2.0-3.0) about 70% of the time. The observed TTR in PREVAIL of 68%. Table 29 compares the TTR in the PREVAIL and PROTECT AF Control Group to that of recent studies.

Table 29: Warfarin TTR in Randomized Control Studies

Study (Treatment)	Warfarin Control Group Mean TTR
PROTECT AF (WATCHMAN)	70%
PREVAIL (WATCHMAN)	68%
RE-LY (Dabigatran)[16]	64%
ARISTOTLE (Apixaban) [18]	62%
ROCKET AF (Rivaroxaban)[17]	55%

9.4 Efficacy Results

9.4.1 PROTECT AF – Efficacy Primary Endpoint

The pre-specified primary analysis cohort includes all randomized patients in the group to which they were assigned and all primary events. Rates are calculated per 100 patient-years of follow-up. There are three data sets of interest in analyzing the efficacy primary endpoint:

- *900 patient-years:* This data set represents the results shown to the Advisory Panel in 2009.

- *1588 patient-years:* This data set is an updated version that was used to contribute prior information to the Bayesian analysis of the PREVAIL study.

- *2621 patient-years:* This data set is the most current and represents the most recent results.

The PROTECT AF and PREVAIL randomized studies and the CAP Registry all had a common efficacy primary endpoint consisting of a composite of stroke (ischemic or hemorrhagic), systemic embolism or cardiovascular/unexplained death.

The PROTECT AF efficacy endpoint presented at the 2009 panel based on 900 patient-years of follow-up met its pre-specified criterion for non-inferiority. The WATCHMAN device was associated with a rate ratio from the Bayesian analysis of 0.68 [95% CrI (0.37, 1.41)] and a posterior probability of 0.998 for non-inferiority. Since that panel meeting, more follow-up data are available to 2621 patient-years of follow-up. The rate ratio based on the current data set was 0.60 [95% CrI (0.40, 1.05)]. Not only was the non-inferiority criterion satisfied with a posterior probability >0.999, but superiority was also achieved with the WATCHMAN Closure Device when compared to warfarin (posterior probability of 0.960).

Figure 15 provides a forest plot of the overall efficacy primary endpoint as well as its components. The corresponding events from the 900 patient-year data set and the current 2621 patient-year data set are shown side-by-side in Table 30 to illustrate the durability of the efficacy with increased follow-up.

Figure 15: PROTECT AF Efficacy Primary Endpoint: Stratified by Component
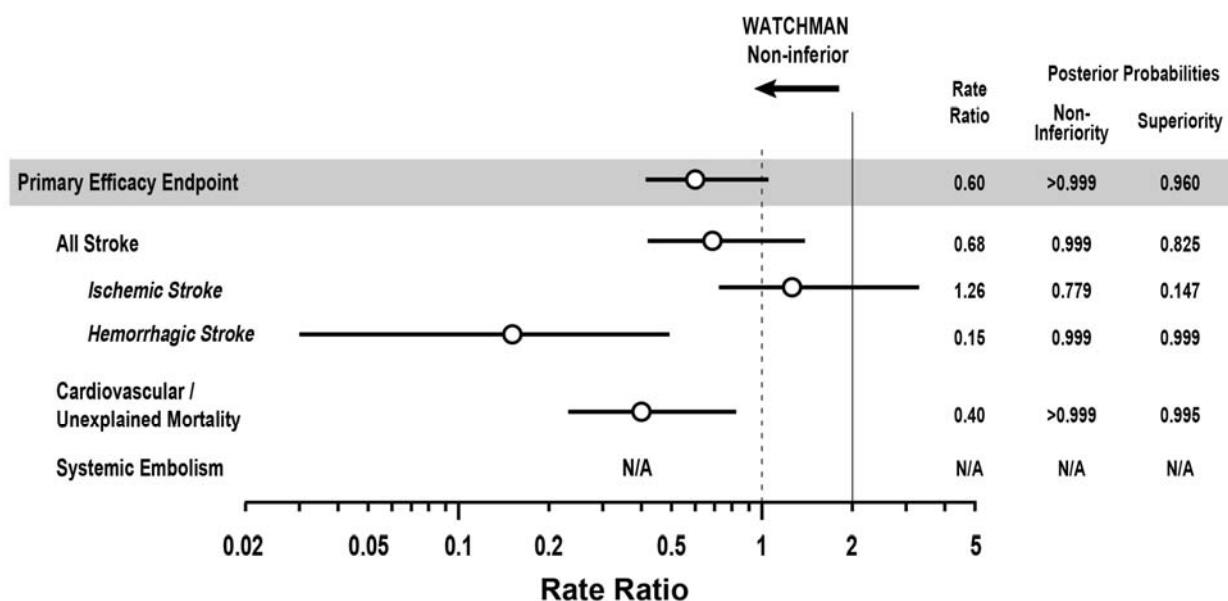
Table 30: PROTECT AF: Efficacy Primary Endpoint Events at 900 and 2621 Patient-Years

Type	PROTECT AF 900 Patient-Years		PROTECT AF 2621 Patient-Years	
	Device (N Events/%)	Control (N Events/%)	Device (N Events/%)	Control (N Events/%)
Stroke - Ischemic	14 (3.0%)	5 (2.0%)	24 (5.2%)	10 (4.1%)
Stroke - Hemorrhagic	1 (0.2%)	6 (2.5%)	2 (0.4%)	10 (4.1%)
Systemic embolism	2 (0.4%)	0 (0.0%)	2 (0.4%)	0 (0.0%)
Death – Cardiovascular and Unexplained	3 (0.6%)	5 (2.0%)	11 (2.4%)	14 (5.7%)

The percentage of patients with an ischemic stroke is higher in the Device Group. The events in this group included one patient who experienced a stroke after randomization but before a device implant was attempted and five patients with procedural strokes resulting from air embolism Removing these procedural events, in order to focus on post procedure stroke rates, the percentage of Device Group patients experiencing an ischemic stroke post-procedure in the 2621 patient-years data set is 3.9% (18/463), which is similar to the Control Group percentage of 4.1%.

Application of the Bayesian analysis to the efficacy primary endpoint is shown in Table 31. Over time, the efficacy primary endpoint consistently demonstrated non-inferiority and ultimately demonstrated superiority.

Table 31: PROTECT AF: Efficacy Primary Endpoint - Results by Patient-Year Intervals

Analysis Cohort	Device		Control		Rate Ratio (95% CrI)		Posterior Probabilities	
	Rate (95% CrI)		Rate (95% CrI)				Non-inferiority	Superiority
900 pt-years	3.4	(2.1, 5.2)	5.0	(2.8, 7.6)	0.68	(0.37, 1.41)	0.998	0.837
1588 pt-years	3.0	(2.1,4.3)	4.3	(2.6, 5.9)	0.71	(0.44, 1.30)	>0.999	0.846
2621 pt-years	2.3	(1.7, 3.2)	3.8	(2.5, 4.9)	0.60	(0.41, 1.05)	>0.999	0.960

Pt-years = patient-years CrI = credible interval
Rate = event rate per 100 patient-years (calculated as 100*N events/Total patient-years)
Rate ratio, calculated as Device rate over Control rate

Kaplan-Meier curves are provided to illustrate the temporal occurrence of events within the PROTECT AF study in Figure 16. Table 32 provides Kaplan-Meier estimates in tabular form for the current data set. The Kaplan-Meier curves in the panel on the left correspond to the data set shown to the Advisory Panel in 2009 while the Kaplan-Meier curves in the panel on the right depict the current data set.

Figure 16: PROTECT AF: Efficacy Primary Endpoint - Kaplan-Meier Curves at 900 and 2621 Patient-Years
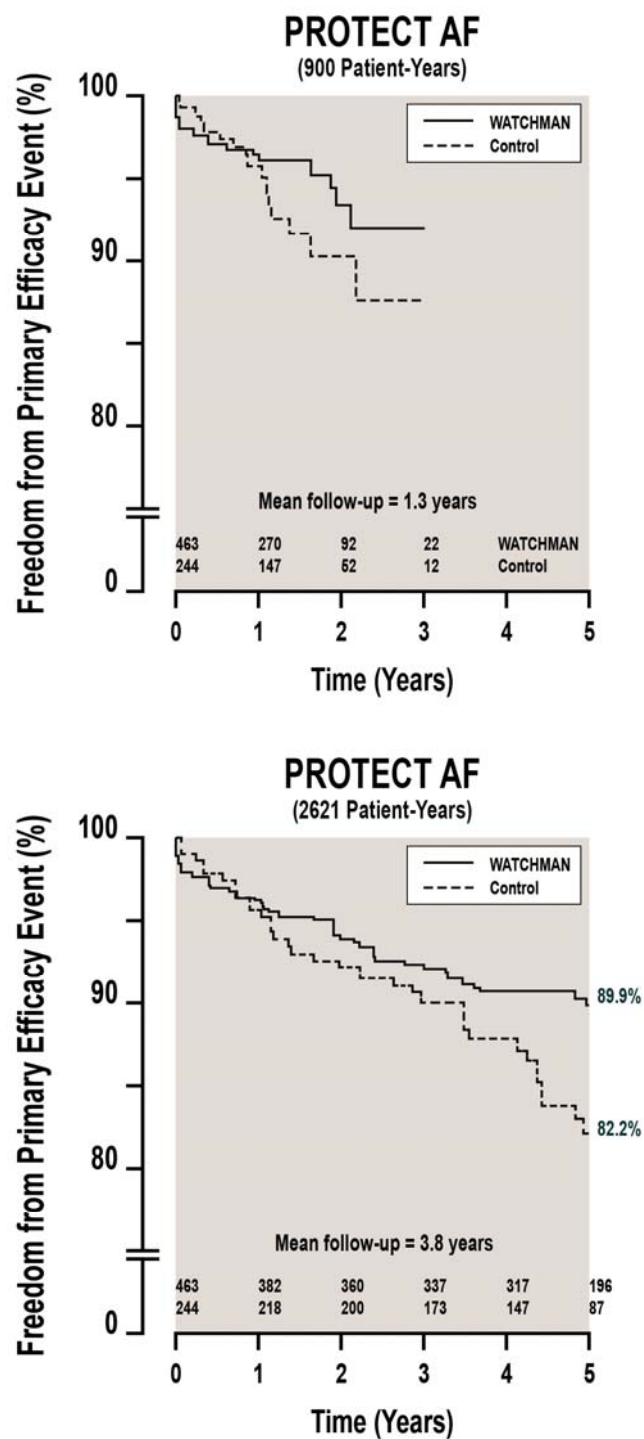
Table 32: PROTECT AF: Efficacy Primary Endpoint - Event-free Rates at 2621 Pt-Yrs

Time Point	Device			Control		
	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)
7-days	7	7	98.5 (96.8, 99.3)	0	0	100.0 (100.0, 100.0)
45-days	2	9	98.0 (96.3, 99.0)	2	2	99.2 (96.7, 99.8)
6-months	4	13	97.1 (95.0, 98.3)	3	5	97.9 (95.1, 99.1)
1-year	3	16	96.3 (94.1, 97.7)	5	10	95.7 (92.2, 97.7)
2-year	9	25	94.0 (91.3, 95.9)	8	18	92.2 (87.9, 95.0)
3-year	7	32	92.1 (89.1, 94.4)	4	22	90.2 (85.4, 93.4)
4-year	5	37	90.8 (87.5, 93.2)	4	26	88.0 (82.8, 91.7)
5-year	2	39	89.9 (86.3, 92.5)	8	34	82.2 (75.6, 87.1)

These efficacy primary endpoint data from PROTECT AF demonstrated the current long-term PROTECT AF analysis of 2621 patient-years, the primary efficacy event rate was 3.8 events/100 patient-years for the Control Group and 2.3 events/100 patient-years for the Device Group, yielding a rate ratio of 0.60. This rate ratio corresponds to a 40% relative reduction in the rate of primary efficacy events in the Device Group with a posterior probability >0.999 for non-inferiority and a posterior probability of 0.960 for superiority. ***The PROTECT AF study met its efficacy primary endpoint for non-inferiority and eventually demonstrated superiority over warfarin.***

9.4.2   PROTECT AF - Components of the Efficacy Primary Endpoint

The most common primary efficacy events were stroke and death (cardiovascular and unexplained). Analyses of these endpoints, including a comparison of rates via the primary Bayesian model, and Kaplan-Meier figures and survival estimates for these components are discussed in the following sections of this report.

9.4.2.1 PROTECT AF - All-Stroke

The mechanism of action of the WATCHMAN device was intended to prohibit the embolization of thrombi from the left atrial appendage, thus reducing ischemic stroke. Additionally, the proposed indication for the device addresses the added benefit of eliminating anticoagulation therapy from patients' drug regimen. Since hemorrhagic stroke can result from hemorrhagic transformation of an initial ischemic event and since anticoagulation therapy has a known risk of hemorrhagic stroke, it is important to evaluate all strokes when assessing if there is a benefit to the Device or Control Group.

The Bayesian results for all-stroke at 1588 and 2621 patient-years are provided in Table 33 and results from Kaplan-Meier analyses for all-stroke are provided in Figure 17 and Table 34.

Table 33: PROTECT AF: All Stroke -Results by Patient-Year Intervals

Data Set	Device			Control			Rate Ratio (95% CrI)	Posterior Probabilities	
	N Patients	N Events/ Total Pt-Yrs	Rate (95% CrI)	N Patients	N Events/ Total Pt-Yrs	Rate (95% CrI)		Non-inferiority	Superiority
900 pt-years	463	15/582.9	2.6 (1.5, 4.1)	244	11/318.1	3.5 (1.7, 5.7)	0.74 (0.36, 1.76)	0.998	0.731
1588 pt-years	463	21/1026.3	2.0 (1.3, 3.1)	244	15/562.7	2.7 (1.5, 4.1)	0.77 (0.42, 1.62)	0.995	0.728
2621 pt-years	463	26/1720.7	1.5 (1.0, 2.2)	244	20/901.2	2.2 (1.3, 3.1)	0.68 (0.42, 1.37)	0.999	0.825

These data demonstrate the following:

- At the current analysis of 2621 pt-years, the stroke rate is 1.5 for the Device Group and 2.2 for the Control Group, yielding a rate ratio of 0.68, or 32% lower rate of stroke in the Device Group compared to the Control Group.

- Each analysis time point shows a rate ratio that benefits the Device Group compared to the Control Group. With longer follow-up the benefit of the Device Group increases.

- The posterior probabilities demonstrate the Device Group achieved non-inferiority over the Control Group for all stroke with 27 months average follow-up (1588 pt-years) and again maintained non-inferiority with longer follow-up at 45 months (2621 pt-years).

- A comparative analysis of all-stroke using the Cox proportional hazards model demonstrated similar results. The efficacy event rate is 1.5/100 pt-years in the Device Group and 2.2/100 pt-years in the Control Group, yielding a hazard ratio of 0.70 (95% CI 0.39, 1.26). The Cox proportional hazard model confirmed non-inferiority of the Device Group over the Control Group for all-stroke.

Figure 17: PROTECT AF: All Stroke - Kaplan-Meier Curves at 2621 Patient-Years
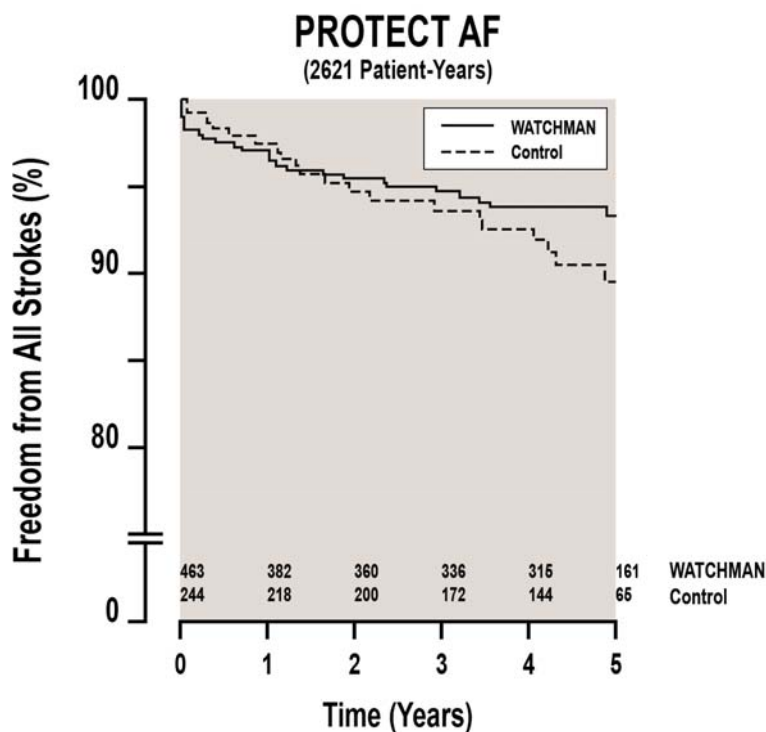
Table 34: PROTECT AF: All Stroke - Event-free Rates at 2621 Pt-Yrs

Time Point	Device			Control		
	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)
7-days	6	6	98.7 (97.1, 99.4)	0	0	100.0 (100.0, 100.0)
45-days	2	8	98.3 (96.5, 99.1)	2	2	99.2 (96.7, 99.8)
6-months	3	11	97.5 (95.6, 98.6)	2	4	98.3 (95.6, 99.4)
1-year	2	13	97.0 (95.0, 98.3)	2	6	97.5 (94.4, 98.8)
2-year	6	19	95.5 (93.0, 97.1)	6	12	94.7 (90.9, 97.0)
3-year	3	22	94.7 (92.0, 96.5)	2	14	93.7 (89.6, 96.2)
4-year	3	25	93.8 (91.0, 95.8)	2	16	92.5 (88.0, 95.4)
5-year	1	26	93.3 (90.3, 95.5)	4	20	89.5 (83.9, 93.2)

9.4.2.2 PROTECT AF - Cardiovascular/Unexplained Death

Cardiovascular and unexplained death was also a major contributor to the efficacy primary endpoint events. Bayesian results are shown in Table 35.

Table 35: PROTECT AF: Cardiovascular/Unexplained Death -Results by Patient-Year Intervals

Data Set	Device		Control		Rate Ratio (95% CI)
	N Events/ Total Pt-Yrs	Rate (95% CI)	N Events/ Total Pt-Yrs	Rate (95% CI)	
1588 pt-years	11/1050.4	1.0 (0.5, 1.8)	14/573.2	2.4 (1.3, 3.8)	0.43 (0.20, 0.99)
2621 pt-years	17/1774.2	1.0 (0.6, 1.5)	22/919.8	2.4 (1.4, 3.4)	0.40 (0.23, 0.82)

These data demonstrate the following:

- At the current analysis of 2621 pt-years, the cardiovascular/unexplained death rate is 1.0 for the Device Group and 2.4 for the Control Group, yielding a rate ratio of 0.40, or 60% lower rate of cardiovascular/unexplained death in the Device Group compared to the Control Group. The posterior probability is >0.999 for non-inferiority and 0.995 for superiority, meaning the Device Group is superior to the Control Group for cardiovascular/unexplained death.

- Each data set shows a similar rate ratio that significantly favors the Device Group compared to the Control Group.

- A comparative analysis of cardiovascular/unexplained death using the Cox proportional hazards model demonstrated similar results. The efficacy event rate is 1.0/100 pt-years in the Device Group and 2.3/100 pt-years in the Control Group, yielding a hazard ratio of 0.40 (95% CI 0.21, 0.75; p=0.0045). The Cox proportional hazard model confirmed non-inferiority and superiority of the Device Group over the Control Group for cardiovascular/unexplained death.

The Kaplan-Meier analysis for cardiovascular/unexplained death is detailed in Figure 18 and Table 36.

Figure 18: PROTECT AF: Freedom from Cardiovascular/Unexplained Death - Kaplan-Meier Curves at 2621 Patient-Years
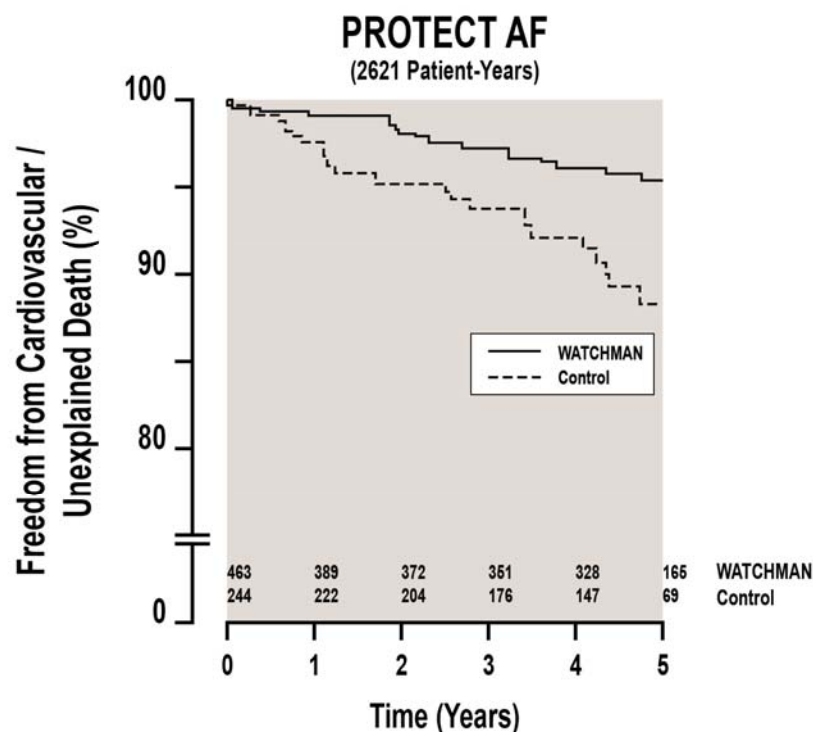
Table 36: PROTECT AF: Cardiovascular/Unexplained Death - Event-free Rates at 2621 Pt-Yrs

	Device			Control		
Time Point	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)
7-days	0	0	100.0 (100.0, 100.0)	0	0	100.0 (100.0, 100.0)
45-days	2	2	99.6 (98.2, 99.9)	1	1	99.6 (97.1, 99.9)
6-months	1	3	99.3 (97.9, 99.8)	1	2	99.2 (96.7, 99.8)
1-year	1	4	99.1 (97.5, 99.6)	4	6	97.4 (94.4, 98.8)
2-year	4	8	98.0 (96.0, 99.0)	5	11	95.2 (91.5, 97.3)
3-year	3	11	97.2 (95.0, 98.4)	3	14	93.7 (89.6, 96.2)
4-year	4	15	96.1 (93.5, 97.6)	3	17	92.0 (87.4, 95.0)
5-year	2	17	95.3 (92.5, 97.1)	5	22	88.3 (82.6, 92.3)

9.4.3 PROTECT AF: Missing Data

Primary analyses were defined to include all available data, and imputation of missing data was not expressly provisioned in the protocol-defined analyses. While study planning and execution was constructed to minimize the amount of missing data, some missing data is present both in the form of limited follow-up on patients randomized to WATCHMAN but not implanted with the device, and in patient attrition over the course of study follow-up. As PROTECT AF has the longer-term follow-up, the issue of missing data is more important and the following focuses on methods and results in that study.

9.4.3.1 Randomized but not Implanted

In PROTECT AF, patients randomized to WATCHMAN but not successfully implanted were not mandated to continue follow-up in the same fashion as implanted patients. However, primary efficacy and safety events for WATCHMAN patients who were not successfully implanted were collected and analyzed as part of the randomized WATCHMAN group. All post-randomization events counted toward these analyses, even, for example, an instance of a primary endpoint event which occurred post-randomization but prior to implant attempt.

In total, there were 55 patients randomized to WATCHMAN in PROTECT AF but not implanted with the device, who had a mean follow-up of 3 months in the trial. There were 41 patients that had an unsuccessful implant attempt (Table 37) and 14 patients that had no implant attempted (Table 38).

Table 37: PROTECT AF: Reasons for Unsuccessful Implant Attempts

Reason for Unsuccessful Implant	N
Unable to meet device release characteristics	22
Sheath unable to access LAA	4
Adverse Event	11
Other	4

Table 38: PROTECT AF: Reasons for No Implant Attempt

Reason for No Implant Attempt	N
No implant within required window post-randomization	10
Withdrawal of consent	2
Death	1
Other	1

For a non-inferiority trial, the primary analysis approach for the non-implanted patients is conservative. For example, imagining an extreme case in which none of the randomized device patients was implanted, all would likely then receive warfarin and be treated identically to control patients. Nearly identical event rates in both groups would then be expected and non-inferiority would be concluded.

Among patients randomized to WATCHMAN but not undergoing successful implant, 3 experienced primary efficacy events and 13 had primary safety events. As noted, all of these events were categorized as WATCHMAN randomized group outcomes and analyzed as such. Most primary safety events in patients in whom implant was attempted but not completed were actually associated with the absence of an implant – that is, the adverse event resulted in the abandonment of the implant attempt.

The primary concern with missing data in a trial of this type is the potential for introduction of bias, such as would potentially be the case if there were substantial differences between the types of patients with attrition versus those without. To mitigate these concerns, Table 39 compares baseline characteristics in the randomized WATCHMAN patients between those implanted and those not. There were no statistically significant differences between these two groups. In particular, the mean $CHADS_2$ scores were 2.2 ± 1.1 (implanted) and 2.3 ± 1.3 (non-implanted).

Table 39: PROTECT AF: Comparison of Demographic Data between Implanted and Non-Implanted Patients

Characteristic	Implant N=408	No Implant N=55	P-value
Age, years	71.7 ± 8.8 (408) (46.0, 95.0)	72.0 ± 8.4 (55) (50.0, 89.0)	0.784
BMI, kg/m^2	31.6 ± 5.9 (407) (14.0, 54.0)	31.5 ± 6.5 (55) (17.0, 47.0)	0.920
Gender			0.587
Female	119/408 (29.2%)	18/55 (32.7%)	
Male	289/408 (70.8%)	37/55 (67.3%)	
Race/Ethnicity			0.437
Caucasian	376/408 (92.2%)	49/55 (89.1%)	
Non-Caucasian	32/408 (7.8%)	6/55 (10.9%)	
CHADS$_2$ Score			0.714
1	137/408 (33.6%)	19/55 (34.6%)	
2	141/408 (34.6%)	17/55 (30.9%)	
3	78/408 (19.1%)	11/55 (20.0%)	
4	34/408 (8.3%)	3/55 (5.5%)	
5	15/408 (3.7%)	4/55 (7.3%)	
6	3/408 (0.7%)	1/55 (1.8%)	
CHADS$_2$ Score (Continuous)	2.2 ± 1.1 (408) (1.0, 6.0)	2.3 ± 1.3 (55) (1.0, 6.0)	0.576
LAA length, mm	30.9 ± 6.3 (402) (17.0, 52.0)	29.3 ± 7.3 (55) (15.3, 50.0)	0.088
LAA ostium diameter, mm	21.5 ± 3.4 (402) (14.0, 33.2)	22.5 ± 4.4 (55) (15.0, 37.1)	0.136
Number of LAA lobes			0.759
One	194/406 (47.8%)	27/54 (50.0%)	
More than one	212/406 (52.2%)	27/54 (50.0%)	

9.4.3.2 *Withdrawals/Lost to Follow-Up*

Patients who voluntarily withdrew from the study early include 6.5% (30/463) of Device patients and 23.0% (56/244) of Control patients. This percentage includes patients who withdrew consent and are lost to follow-up. Similar to failed implant, comparing baseline characteristics in the randomized patients between those lost to attrition during study follow-up and those that did

not, there were no significant differences. These baseline differences are summarized in Table 40.

Table 40: PROTECT AF: Comparison of Demographic Data between Patients Exiting Early and Patients Not Exiting Early

Characteristic	Early Exit N=86	No Early Exit N=621	P-value
Age, years	71.8 ± 10.5 (86) (41.0, 89.0)	72.1 ± 8.7 (621) (45.0, 95.0)	0.753
BMI, kg/m^2	31.1 ± 5.4 (86) (17.0, 46.0)	31.5 ± 6.1 (620) (14.0, 57.0)	0.506
Gender			0.536
Female	28/86 (32.6%)	182/621 (29.3%)	
Male	58/86 (67.4%)	439/621 (70.7%)	
Race/Ethnicity			0.052
Caucasian	74/86 (86.1%)	573/621 (92.3%)	
Non-Caucasian	12/86 (13.9%)	48/621 (7.7%)	
CHADS$_2$ Score			0.636
1	29/86 (33.7%)	193/621 (31.1%)	
2	21/86 (24.4%)	225/621 (36.2%)	
3	29/86 (33.7%)	111/621 (17.9%)	
4	6/86 (7.0%)	55/621 (8.9%)	
5	1/86 (1.2%)	28/621 (4.5%)	
6	0/86 (0.0%)	9/621 (1.5%)	
CHADS$_2$ Score (Continuous)	2.2 ± 1.0 (86) (1.0, 5.0)	2.2 ± 1.2 (621) (1.0, 6.0)	0.637
LAA length, mm	30.8 ± 7.0 (84) (15.3, 49.0)	30.7 ± 6.6 (612) (7.0, 61.5)	0.859
LAA ostium diameter, mm	21.7 ± 3.5 (84) (15.0, 31.8)	21.8 ± 3.6 (612) (14.0, 37.1)	0.826
Number of LAA lobes			0.602
One	40/86 (46.5%)	305/616 (49.5%)	
More than one	46/86 (53.5%)	311/616 (50.5%)	

Since this type of attrition was most prevalent in the control group, a sensitivity analysis of the efficacy primary endpoint in PROTECT AF was conducted. For the 56 control patients with early attrition, the sensitivity analysis considered patients among these 56 without events to have completed 5-year follow-up without experiencing an event. That is, this represents a conservative scenario that removes potential bias by effectively decreasing the Control Group event rate. The results of the sensitivity analysis showed a risk ratio of 0.69 (versus 0.60 in the

primary effectiveness analysis), with a non-inferiority posterior probability of 0.999 and a superiority posterior probability of 0.880. Thus even this worst-case scenario for potential long-term attrition bias preserves the finding of non-inferiority for WATCHMAN versus warfarin in primary effectiveness.

9.4.4 PROTECT AF - Secondary Outcomes

There were three pre-specified secondary analyses of the primary endpoint. These analyses were performed based on the PROTECT AF study data set with 2621 patient-years of follow-up and are described as follows:

- **Post-procedure:** Evaluates the safety and efficacy of the device following attempted implant of the WATCHMAN device. Device patient follow-up time begins at the date of implant as opposed to the date of randomization. There were no exclusions in the Control Group.

- **Per-protocol:** Evaluates the safety and efficacy of the device for patients who received their assigned therapy. Device patients who were successfully implanted with the device and discontinued warfarin therapy and Control patients who were taking warfarin at baseline or 45-days are included in this analysis. Device patient follow-up time begins from the date of first warfarin cessation.

- **Terminal Therapy:** Evaluates the safety and efficacy of the device for patients who received their assigned therapy. Device patients who were successfully implanted with the device and discontinued warfarin and/or clopidogrel therapy and Control patients who were taking warfarin at baseline or 45-days are included in this analysis. Device patient follow-up time begins from the date of clopidogrel cessation.

The Bayesian analyses for the primary efficacy analysis and the three secondary analyses are shown in Table 41.

Table 41: PROTECT AF: Bayesian Analysis of Primary Efficacy by Secondary Analysis Cohort (2621 Pt-Yrs)

Analysis Cohort	Device		Control		Primary Efficacy Risk Ratio (95% CrI)	Posterior Probabilities	
	N Events/ Total Pt-Yrs	Rate (95% CrI)	N Events/ Total Pt-Yrs	Rate (95% CrI)		Non-inferiority	Superiority
Primary Analysis	39/1720.1	2.3 (1.7, 3.2)	34/901.2	3.8 (2.5, 4.9)	0.60 (0.41, 1.05)	>0.999	0.960
Post-Procedure	33/1710.0	1.9 (1.4, 2.8)	34/901.2	3.8 (2.5, 4.9)	0.51 (0.35, 0.92)	>0.999	0.990
Per-Protocol	29/1614.4	1.8 (1.4, 2.7)	33/900.6	3.7 (2.4, 4.9)	0.50 (0.34, 0.91)	>0.999	0.990
Terminal Therapy	24/1311.1	1.8 (1.3, 2.8)	33/900.2	3.7 (2.4, 4.8)	0.50 (0.32, 0.94)	>0.999	0.985

After the implant procedure, the rate of primary efficacy events decreased from 2.3 to 1.9 events per 100 pt-years. This rate remains stable in long-term follow-up at 1.8 per 100 pt-years after the cessation of warfarin and clopidogrel therapy. As expected, the Control Group rate is similar for each analysis cohort. These additional analysis cohorts demonstrate a reduction in the rate ratio from 0.60 in the primary efficacy cohort compared to 0.50 after the cessation of warfarin and clopidogrel in the Device Group. This translates to a 40% to 50% lower rate of efficacy events in the Device Group compared to the Control Group.

In all analysis cohorts, the Device Group is non-inferior to the Control Group. In all analyses, cohort superiority of the Device Group to the Control Group is achieved where the posterior probability is defined as greater than 0.95.

9.4.5   Long-Term PROTECT AF Analysis Conclusions

The long-term PROTECT AF study corroborates the analysis presented at the 2009 Advisory Panel Meeting. The WATCHMAN Closure Device demonstrated a 40% relative reduction in the rate ratio of the primary composite endpoint.

Analysis of the individual components of the primary endpoint revealed that the WATCHMAN device performed similarly to warfarin in reducing the risk of ischemic stroke and was superior to warfarin in reducing hemorrhagic stroke and cardiovascular death.

9.4.6 PREVAIL – Efficacy Primary Endpoint

9.4.6.1 Description of Cohort

The pre-specified analysis cohort includes all randomized patients in the group to which they were assigned and all primary events. Calculations of credible intervals are from the Bayesian model as described in the Statistical Analysis Plan. Data presented in the following sections include prior data from the PROTECT AF and CAP trials per the SAP in the primary endpoint results tables, but only PREVAIL patient level data in the lists of events contributing to the endpoints. The analysis occurred after all enrolled patients completed their 6-month visit; therefore, all enrolled patients were in the post 182-day time period.

9.4.6.2 Efficacy Primary Endpoint

The first primary endpoint was analyzed using a Bayesian piecewise exponential model with the historical priors based on data from the previous pivotal study PROTECT AF. This was a non-inferiority design with comparison of rate ratio of 18-month event rates of the Device and Control Groups. The 18-month rate represents the modeled probability of an event occurring within 18 months, and the 18-month rate ratio is a mean of the rate ratios. All follow-up information from the post-182 day time period contributes to the final hazards in the model (i.e. the risk of events post-182 days) and contributes to the calculation of the probability of an event at 18 months. Results for the efficacy primary endpoint of stroke, death (cardiovascular or unexplained) and systemic embolism are displayed in Table 42.

Table 42: PREVAIL: Efficacy Primary Endpoint

Device 18-Month Rate	Control 18-Month Rate	18-Month Rate Ratio (95% CrI)	Rate Ratio Non-Inferiority Criterion
0.064	0.063	1.07 (0.57, 1.89)	95% CrI Upper Bound < 1.75

CrI = credible interval

There were similar modeled 18-month event rates in the Device and Control Groups. The 18-month rate was 0.064 for the Device Group and 0.063 for the Control Group. These rates yielded a mean 18-month rate ratio of 1.07 with a 95% credible interval of 0.57 to 1.89. The upper bound of 1.89 was not lower than the non-inferiority margin of 1.75 defined in the statistical analysis plan, therefore statistical non-inferiority was not achieved.

The PREVAIL study was designed based on an adaptive sample size with a final analysis planned after 6 months of follow-up after the closure of enrollment. The current analysis of the efficacy primary endpoint is based on this planned final analysis and contains the same primary endpoint components as the PROTECT AF study.

Longer term follow-up is available on the PROTECT AF cohort, with an average follow-up of over 45 months, compared to an average of just under 1 year at the time of the first PMA submission in August 2008. The longer term results from PROTECT AF are consistent with the original findings of non-inferiority for the same composite primary endpoint; the current rate ratio is 0.60 and the credible interval upper bound is 1.05. Additionally the Kaplan-Meier analysis for the efficacy primary endpoint from PROTECT AF shows the longer term favorable results, with curves for the randomized groups showing separation in the post 12 month period. Given this large data set with substantial long-term follow-up, and the more limited sample size of the PREVAIL data, it is unlikely that additional follow-up data from PREVAIL would substantially alter the conclusions of the totality of the data, which is the device demonstrates long-term non-inferiority compared to warfarin for the composite efficacy primary endpoint.

Table 43 summarizes the specific components of the efficacy primary endpoint events by randomized group.

Table 43: PREVAIL: Efficacy Primary Endpoint Events

Endpoint Event Type	Device Group		Control Group	
	N Events	% of Patients	N Events	% of Patients
Stroke-Ischemic	5	1.9	1	0.7
Stroke-Hemorrhagic	1	0.4	0	0.0
Systemic Embolism	1	0.4	0	0.0
Death (Cardiovascular or Unexplained)	7	2.6	3	2.2

Results from Kaplan-Meier analyses for the efficacy primary endpoint are provided in Figure 19 and Table 44.

Figure 19: PREVAIL: Efficacy Primary Endpoint – Kaplan-Meier Curves
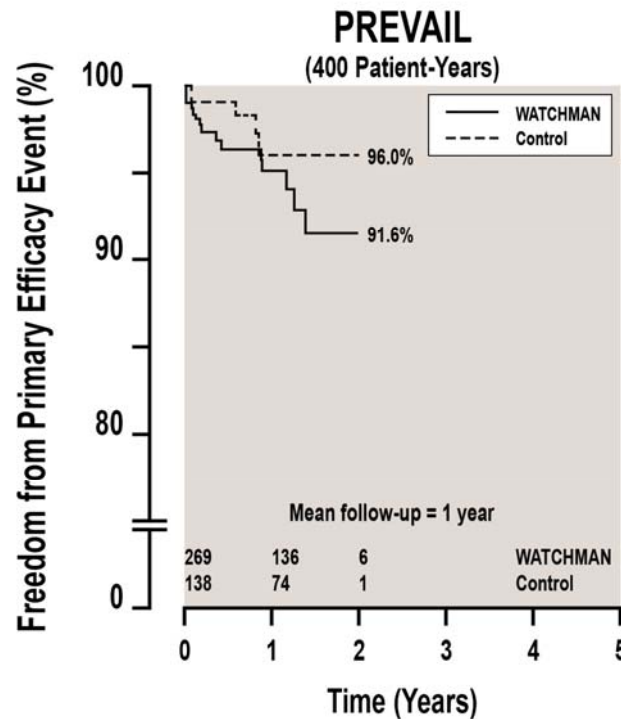
Table 44: PREVAIL: Efficacy Primary Endpoint

Time Point	Device Group			Control Group		
	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)
7-days	2	2	99.2 (97.0, 99.8)	0	0	100.0 (100.0, 100.0)
45-days	2	4	98.5 (96.0, 99.4)	1	1	99.3 (95.0, 99.9)
6-months	5	9	96.5 (93.4, 98.2)	0	1	99.3 (95.0, 99.9)
1-year	2	11	95.3 (91.5, 97.4)	3	4	96.0 (89.6, 98.5)
2-year	3	14	91.6 (85.1, 95.3)	0	4	96.0 (89.6, 98.5)

The largest portion of the primary endpoint for the Device Group (5/14, 36%) occurred between 45 days and 6 months. The largest portion of the efficacy primary endpoint for the Control Group (3/4, 75%) occurred between 6 months and one year post-randomization.

9.4.6.3 Evaluation of Efficacy Primary Endpoint by Component

The efficacy primary endpoint, which was the composite of ischemic stroke, hemorrhagic stroke, systemic embolism, and death (cardiovascular or unexplained) was evaluated by individual components for this analysis. These event rates were analyzed using the same Bayesian model as the composite efficacy primary endpoint. Table 45 summarizes the individual components of the efficacy primary endpoint by randomized group. Each component of the endpoint showed similar 18-month rates in the Device and Control Groups, however, the Device Group was statistically non-inferior to the Control Group in the components of hemorrhagic stroke and cardiovascular/unexplained death. The largest contributing component in the efficacy primary endpoint was cardiovascular/unexplained death, resulting in an 18-month rate of 0.03 in the Device Group and 0.04 in the Control Group with an 18-month rate ratio of 0.68 favoring the Device Group.

Table 45: PREVAIL: Bayesian Model Results: Components of Efficacy Primary Endpoint

Randomization Allocation (2 Device: 1 Control)

Component of Efficacy Primary Endpoint	Device Group 18-Month Rate (95% CrI)	Control Group 18-Month Rate (95% CrI)	Bayesian 18-Month Rate Ratio (95% CrI)
Stroke - Ischemic	0.03 (0.02, 0.05)	0.02 (0.01, 0.04)	2.05 (0.67, 5.27)
Stroke - Hemorrhagic	0.01 (0.00, 0.03)	0.03 (0.01, 0.06)	0.48 (0.13, 1.20)
Systemic Embolism	0.02 (0.01, 0.04)	0.02 (0.00, 0.04)	1.97 (0.52, 5.79)
Death (Cardiovascular or Unexplained)	0.03 (0.01, 0.04)	0.04 (0.02, 0.07)	0.68 (0.27, 1.43)

Additionally, the statistical analysis plan required a summary of the components of the endpoint. This summary is shown in Table 44. One of the primary differences in this analysis is that the prior pivotal study data were not used in the calculation; only PREVAIL patient data were included in the model.

Table 46: PREVAIL: Components of Efficacy Primary Endpoint

Randomization Allocation (2 Device: 1 Control)

Component of Efficacy Primary Endpoint	PREVAIL Device Group		PREVAIL Control Group	
	N Events	N Events/ Total Pt-Yrs (Rate)	N Events	N Events/ Total Pt-Yrs (Rate)
Stroke - Ischemic	5	5/257.1 (1.94)	1	1/140.1 (0.71)
Stroke - Hemorrhagic	1	1/259.0 (0.39)	0	0/140.8 (0.00)
Systemic Embolism	1	1/259.6 (0.39)	0	0/140.8 (0.00)
Death (Cardiovascular or Unexplained)	7	7/259.7 (2.70)	3	3/140.8 (2.13)

Rate per 100 pt-years = Event rate per 100 patient-years

Kaplan-Meier analyses were performed for each component of the efficacy primary endpoint for patients enrolled in PREVAIL. Results from the Kaplan-Meier analysis for ischemic stroke are provided in Figure 20 and Table 47.

Figure 20: PREVAIL: Ischemic Stroke – Kaplan-Meier Curves
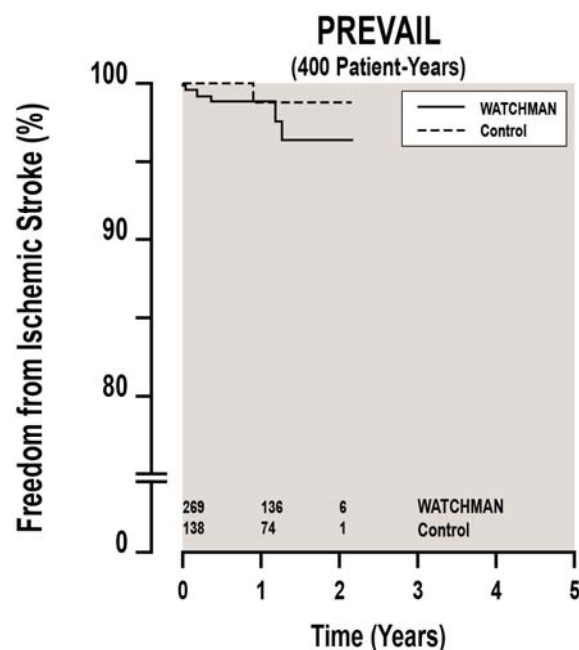
Table 47: PREVAIL: Ischemic Stroke - Kaplan-Meier Estimates

Randomization Allocation (2 Device: 1 Control)

	Device			Control		
Time Point	**N Events**	**N Cumulative Events**	**Event Free Rate (%) (95% CI)**	**N Events**	**N Cumulative Events**	**Event Free Rate (%) (95% CI)**
7-days	1	1	99.6 (97.4, 99.9)	0	0	100.0 (100.0, 100.0)
45-days	0	1	99.6 (97.4, 99.9)	0	0	100.0 (100.0, 100.0)
6-months	2	3	98.8 (96.4, 99.6)	0	0	100.0 (100.0, 100.0)
1-year	0	3	98.8 (96.4, 99.6)	1	1	98.8 (91.8, 99.8)
2-year	2	5	96.3 (90.2, 98.6)	0	1	98.8 (91.8, 99.8)

There were five (5) ischemic strokes in the Device Group and one (1) in the Control Group. Three of the five (3/5) Device Group strokes occurred within the first six months while patients were on warfarin or dual antiplatelet therapy. At one year, the event free rate for the Device and Control Groups were the same.

Results from Kaplan-Meier analysis for hemorrhagic stroke in PREVAIL patients are provided in Figure 21 and Table 48.

Figure 21: PREVAIL: Hemorrhagic Stroke - Kaplan-Meier Curves
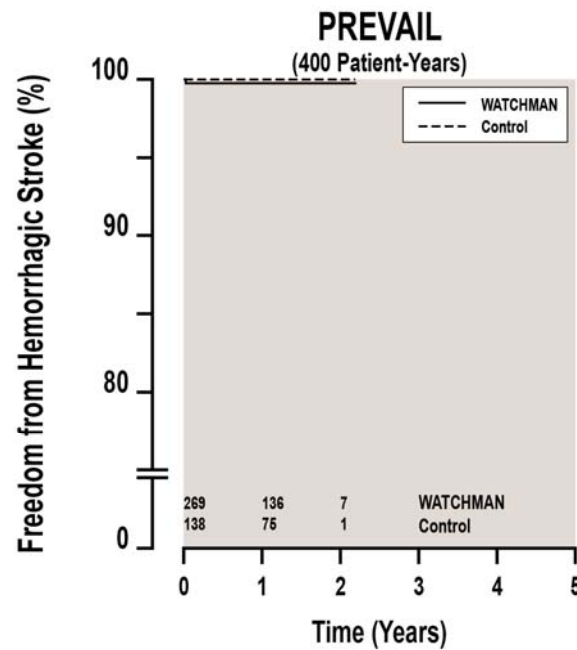
Table 48: PREVAIL: Hemorrhagic Stroke - Kaplan-Meier Estimates

Randomization Allocation (2 Device: 1 Control)

	Device			Control		
Time Point	**N Events**	**N Cumulative Events**	**Event Free Rate (%) (95% CI)**	**N Events**	**N Cumulative Events**	**Event Free Rate (%) (95% CI)**
7-days	1	1	99.6 (97.4, 99.9)	0	0	100.0 (100.0, 100.0)
45-days	0	1	99.6 (97.4, 99.9)	0	0	100.0 (100.0, 100.0)
6-months	0	1	99.6 (97.4, 99.9)	0	0	100.0 (100.0, 100.0)
1-year	0	1	99.6 (97.4, 99.9)	0	0	100.0 (100.0, 100.0)
2-year	0	1	99.6 (97.4, 99.9)	0	0	100.0 (100.0, 100.0)

There was only one hemorrhagic stroke in the PREVAIL study which occurred in the Device Group while the patient was on warfarin therapy.

Results from Kaplan-Meier analysis for systemic embolism in PREVAIL patients are provided in Figure 22 and Table 49.

Figure 22: PREVAIL: Systemic Embolism: Kaplan-Meier Curves
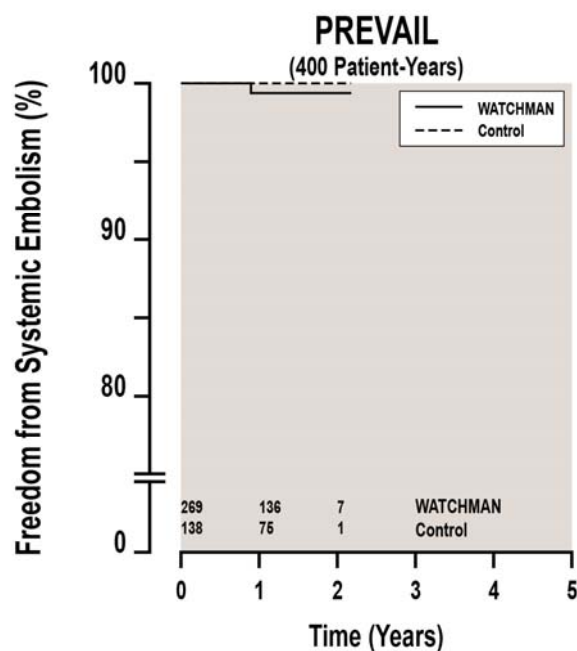
Table 49: PREVAIL: Systemic Embolism - Kaplan-Meier Estimates

Randomization Allocation (2 Device: 1 Control)

Time Point	Device			Control		
	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)
7-days	0	0	100.0 (100.0, 100.0)	0	0	100.0 (100.0, 100.0)
45-days	0	0	100.0 (100.0, 100.0)	0	0	100.0 (100.0, 100.0)
6-months	0	0	100.0 (100.0, 100.0)	0	0	100.0 (100.0, 100.0)
1-year	1	1	99.3 (95.5, 99.9)	0	0	100.0 (100.0, 100.0)
2-year	0	1	99.3 (95.5, 99.9)	0	0	100.0 (100.0, 100.0)

There was only one systemic embolism in the PREVAIL study which occurred in the Device Group.

Results from Kaplan-Meier analyses for cardiovascular/unexplained death in PREVAIL patients are provided in Figure 23 and Table 50.

Figure 23: PREVAIL: Cardiovascular/Unexplained Death – Kaplan-Meier Curves
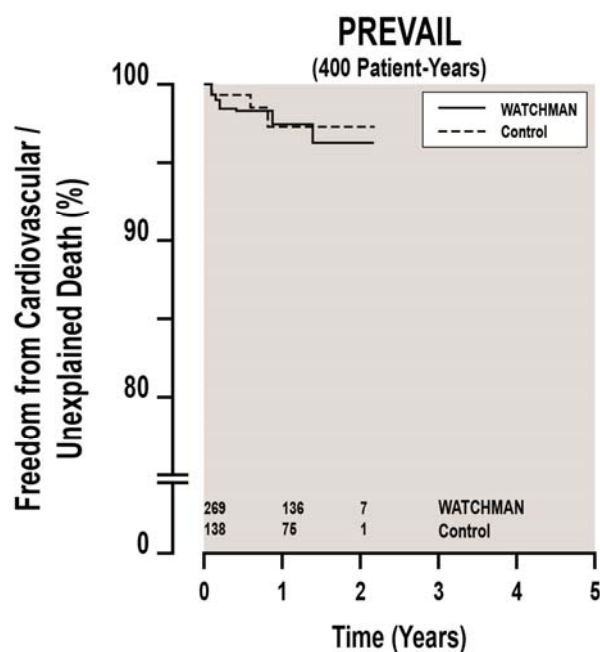
Table 50: PREVAIL: Cardiovascular/Unexplained Death - Kaplan-Meier Estimates

Randomization Allocation (2 Device: 1 Control)

Time Point	Device			Control		
	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)
7-days	0	0	100.0 (100.0, 100.0)	0	0	100.0 (100.0, 100.0)
45-days	2	2	99.2 (97.0, 99.8)	1	1	99.3 (95.0, 99.9)
6-months	3	5	98.1 (95.4, 99.2)	0	1	99.3 (95.0, 99.9)
1-year	1	6	97.4 (94.3, 98.9)	2	3	97.2 (91.4, 99.1)
2-year	1	7	96.1 (91.1, 98.3)	0	3	97.2 (91.4, 99.1)

There were seven (7) cardiovascular/unexplained deaths in the Device Group and three (3) in the Control Group. Five of the seven (5/7) Device Group cardiovascular deaths occurred within the first six months while patients were on warfarin or dual antiplatelet therapy. At one year, the event free rate of cardiovascular/unexplained death for the Device Group and Control Group were similar.

9.4.6.4 Evaluation of Primary Endpoint Results

While the 18-month rates in the Device Group and Control Group were similar (0.064, 0.063), the 95% upper credible interval (1.89) was over the pre-defined upper credible bound (1.75). Therefore, non-inferiority was not statistically achieved which led to an evaluation of possible rationales.

In the PROTECT AF study, the same composite efficacy endpoint of all stroke, cardiovascular or unexplained death and systemic embolism was defined. A Bayesian model was used for analysis but the pre-defined upper credible bound was 2.0 in that study. Moreover, PROTECT AF continued to demonstrate non-inferiority of the Device Group to the Control Group for this efficacy primary endpoint at each of the subsequent analysis time points, and currently superiority has been demonstrated (approximately 45 months of follow-up).

Additionally, the behavior of the treatment groups was evaluated. The noticeable difference in the treatment groups between PREVAIL and PROTECT AF was the lack of endpoint events in the PREVAIL Control Group. In PROTECT AF, there were 13.9% (34/244) of Control patients with an endpoint event in the 1588 pt-year data set; compared to 2.9% (4/138) of patients with an endpoint event in the PREVAIL (400 patient-year data set) Control Group.

The long-term PROTECT AF with its longer follow-up duration provides a better indication of efficacy of the WATCHMAN Closure Device. Both the long-term PROTECT AF results, in the primary efficacy and per-protocol analyses, provide results consistent with the original findings of non-inferiority for the efficacy primary endpoint. The per protocol analysis in particular captures the post-warfarin therapy for device patients and these results are more favorable than the primary efficacy analysis. Furthermore, the PROTECT AF demonstrated non-inferiority and superiority for the same composite efficacy endpoint when patients were followed long term.

9.4.7 PREVAIL - *Mechanism of Action Primary Endpoint*

The mechanism of action primary endpoint was the composite endpoint of ischemic stroke or systemic embolism, excluding events occurring in the first 7 days following randomization. Results for the mechanism of action primary endpoint are displayed in Table 51. Credible intervals were calculated from the same Bayesian model used for the efficacy primary endpoint. The modeled 18-month rate is the probability of an event occurring within 18 months; and the 18- month rate ratio is a mean of the rate ratios. Success on the mechanism of action primary endpoint was based on a criterion for either the risk ratio or risk difference. Extensive simulations were performed as part of the study design under a variety of assumptions about the event rates in each treatment group. As part of these, the probability of success for the mechanism of action primary endpoint for the risk ratio and risk difference was calculated. Under the scenarios examined equivalent to various alternative hypotheses, the probability of success on the risk difference ranged from 0.74 to 0.93 while the probability of success on the risk ratio ranged from 0.16 to 0.27. Thus, only success for the risk difference was expected with high confidence; there was little expectation for success on the risk ratio for this endpoint.

Table 51: PREVAIL: Mechanism of Action Primary Endpoint Results

Device 18-Month Rate	Control 18-Month Rate	18-Month Rate Ratio (95% CrI)	Rate Ratio Non-Inferiority Criterion	18-Month Rate Difference (95% CrI)	Rate Difference Non-Inferiority Criterion
0.0253	0.0200	1.6 (0.5, 4.2)	95% CrI Upper Bound < 2.0	0.0053 (-0.0190, 0.0273)	95% CrI Upper Bound < 0.0275

The modeled 18-month rate was 0.0253 for the Device Group and 0.0200 for the Control Group. The non-inferiority criterion pre-defined in the statistical analysis plan allowed for one of the two following scenarios to statistically achieve non-inferiority of the mechanism of action primary endpoint:

1. The 18-month rate difference must have a 95% upper credible interval less than 0.0275.

<div align="center">OR</div>

2. The 18-month rate ratio had to have a 95% upper credible interval less than 2.0.

The second condition was not met since the upper 95% CrI of 4.2 exceeded the boundary of 2.0. However, the 18-month rate difference was 0.0053 with an upper bound of 0.0273, which met the first condition. Only one of the two criteria needed to be met, therefore the non-inferiority

criterion was achieved. The 18-month rate difference was 0.0053 with an upper bound of 0.0273, therefore achieving the non-inferiority criterion. Non-inferiority of the Device Group to the Control Group was achieved for the mechanism of action primary endpoint of ischemic stroke or systemic embolism greater than 7 days post randomization. Table 52 summarizes the types of mechanism of action primary endpoint events occurring in randomized patients in the PREVAIL study.

Table 52: PREVAIL: Mechanism of Action Primary Endpoint Events

Endpoint Event	Device Group			Control Group		
	N Events	% of Patients	% of Endpoints	N Events	% of Subjects	% of Endpoints
Stroke-Ischemic	4	1.5	80.0	1	0.7	100.0
Systemic Embolism	1	0.4	20.0	0	0.0	0.0

There were only six events in the PREVAIL study which contributed to the mechanism of action primary endpoint. Two events occurred between the 45-day and 6-month visits and the remaining four events occurred after the 6-month visit.

Results from Kaplan-Meier analyses for the mechanism of action primary endpoint are provided in Figure 24 and Table 53.

Figure 24: PREVAIL: Mechanism of Action Primary Endpoint – Kaplan-Meier Curves
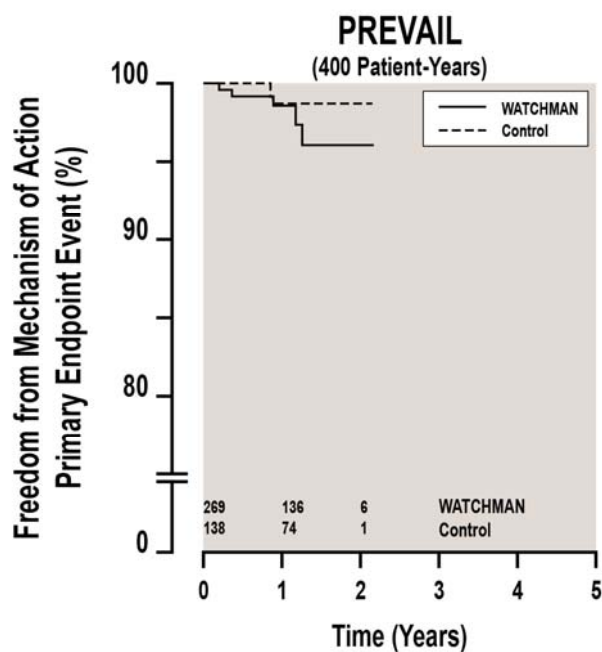
Table 53: PREVAIL: Mechanism of Action Primary Endpoint – Event-free Rates

Time Point	Device			Control		
	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)
45-days	0	0	100.0 (100.0, 100.0)	0	0	100.0 (100.0, 100.0)
6-months	2	2	99.2 (96.8, 99.8)	0	0	100.0 (100.0, 100.0)
1-year	1	3	98.5 (95.4, 99.5)	1	1	98.8 (91.8, 99.8)
2-year	2	5	96.1 (89.8, 98.5)	0	1	98.8 (91.8, 99.8)

The largest portion of mechanism of action primary endpoint events for the Device Group was between 45 days and 6 months and between one and two years. The one event in the Control Group occurred between 6 months and one year post-randomization. At one year, the Device

Group had a Kaplan-Meier estimated event rate of 1.5% compared to a 1.2% event rate in the Control Group.

9.4.8 PREVAIL Analysis Conclusions

The pre-specified primary analysis cohort included all randomized patients in the group to which they were assigned. The following conclusions are made from analysis of the three primary endpoints:

- The efficacy primary endpoint demonstrated similar 18-month event rates in the Device and Control Groups. Despite this the upper bound of the 95% credible interval was 1.89, just above the pre-defined criterion of 1.75, which resulted in not achieving statistical non-inferiority.
    - The same endpoint in the PROTECT AF study with over 45 months of average patient follow-up demonstrated continued non-inferiority and has now confirmed superiority of the Device Group to the Control Group

    - The PREVAIL Control Group has outperformed other contemporary randomized clinical studies with an extremely low rate of ischemic stroke and systemic embolism

    - The PREVAIL Control Group was well managed in terms of protocol compliance with similar or lower rates of warfarin cessation and higher time in therapeutic range compared with recent novel oral anticoagulant drug studies.

- Non-inferiority of the Device Group to the Control Group was achieved for the mechanism of action primary endpoint of ischemic stroke or systemic embolism greater than 7 days post randomization.

9.5 Safety Results

9.5.1 PROTECT AF

The primary safety endpoint was treatment without the occurrence of life-threatening events as determined by the Clinical Events Committee, including events such as device embolization requiring retrieval, bleeding events such as pericardial effusion requiring drainage, cranial bleeding events due to any source, gastrointestinal bleeds requiring transfusion and any bleeding related to the device or procedure that necessitates an operation. No hypothesis was associated with the primary safety endpoint. The safety results are shown in Table 54

Table 54: PROTECT AF: Primary Safety Results

Data Set	Device			Control			Rate Ratio (95% CrI)
	N Patients	N Events/ Total Pt-Yrs	Rate (95% CrI)	N Patients	N Events/ Total Pt-Yrs	Rate (95% CrI)	
900 pt-years	463	48/554.2	8,7 (6.4, 11.3)	244	13/312.0	4.2 (2.2, 6.7)	2.08 (1.48, 6.43)
1588 pt-years	463	54/979.9	5.5 (4.2, 7.1)	244	20/554.6	3.6 (2.2, 5.3)	1.53 (0.95, 2.70)
2621 pt-years	463	60/1666.2	3.6 (2.8, 4.6)	244	27/878.5	3.1 (2.0, 4.3)	1.17 (0.78, 1.96)

These data show the following:

- At 2621 pt-years the primary safety endpoint rate was 3.6% for the Device Group and 3.1% for the Control Group, yielding a rate ratio of 1.17 (95% CrI 0.78, 1.96).

- The Control Group rate was similar at each of the analysis time points whereas the Device Group rate decreased with subsequent time points. A higher rate of early primary safety events in the Device Group compared to the Control Group was expected due to the invasive nature of the implant procedure. The majority of primary safety events in the Device Group (32/60, 53.3%) occurred peri-procedurally.

This outcome indicates that risks in the Device Group were comparable to those seen in the Control Group.

Details of the events adjudicated by the CEC as serious and non-serious are shown in Table 55. The principal procedural related safety events in the Device Group were pericardial effusions, which are a known complication of intracardiac procedures. The rate of pericardial effusions decreased over the course of the study attributable to investigator experience; none had lasting clinical complications.

Table 55: PROTECT AF: Safety Primary Endpoint Events

	Device		Control	
Type	**N Events**	**% of Randomized Patients**	**N Events**	**% of Randomized Patients**
Gastrointestinal Bleeding	14	3.0%	16	6.6%
Pericardial Effusion with Cardiac Tamponade	12	2.6%	0	0.0%
Cardiac Perforation	7	1.5%	0	0.0%
Stroke – Ischemic	6	1.3%	0	0.0%
Cranial Bleed	4	0.9%	1	0.4%
Device Embolization	3	0.6%	0	0.0%
Stroke – Hemorrhagic	3	0.6%	9	3.7%
Other Study Related	3	0.6%	0	0.0%
Pericardial Effusion-Serious	3	0.6%	0	0.0%
Major Bleed Requiring Transfusion	2	0.4%	0	0.0%
Bruising – Hematoma	1	0.2%	0	0.0%
Epistaxis	1	0.2%	0	0.0%
Arrhythmias (temporary asystole)	1	0.2%	0	0.0%
Anemia Requiring Transfusion	0	0.0%	1	0.4%

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9.5.2   CAP Registry

The CAP Registry followed patients receiving the WATCHMAN Closure Device using the same safety endpoint definition as used in PROTECT AF. Safety events adjudicated as related to the procedure or device within 7 days after implant are summarized in Table 56.

These events met the safety endpoint definition for life-threatening or resulting in blood transfusion or surgical intervention.

Table 56: CAP Registry: 7-Day Procedure/Device Related Safety Events

Event Type	N Events	N Patients	% of Patients
Pericardial Effusion with Cardiac Tamponade	7	7	1.2%
Other Study Related	5	5	0.9%
Major Bleed Requiring Transfusion	3	3	0.5%
Pseudoaneurysm	2	2	0.4%
Ventricular Tachyarrhythmia	2	2	0.4%
Anemia Requiring Transfusion	1	1	0.2%
Cardiac Perforation	1	1	0.2%
Device Embolization	1	1	0.2%
Prolonged Bleeding from a Laceration	1	1	0.2%

The most frequent procedure related complication was pericardial effusion with tamponade requiring percutaneous drainage. There were seven (7/566) pericardial effusions with cardiac tamponade treated by percutaneous drainage and one (1/566) cardiac perforation requiring surgical intervention for a total of eight (8/566) procedure/device safety endpoint pericardial effusions reported in the study calculating to 1.4% of patients.

9.5.3   PREVAIL

The primary safety endpoint in PREVAIL was defined as the occurrence of one of the following events between the time of randomization and within 7 days of the procedure or by hospital discharge, whichever is later: all-cause death, ischemic stroke, systemic embolism, or device or procedure related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair. Percutaneous catheter drainage of pericardial effusions, snaring of an embolized device, thrombin injection to treat femoral pseudoaneurysm and nonsurgical treatments of access site complications were excluded from this endpoint. This endpoint was analyzed for patients randomized to the Device Group only.

Results for the primary safety endpoint are displayed in Table 57. Credible intervals were calculated from a Bayesian model utilizing data from PROTECT AF and CAP Registry as prior information and calculation of first event per patient.

Table 57: PREVAIL: Safety Primary Endpoint Results

Device Group		
N Patients	% (n/N)	95% CrI
269	2.2% (6/269)	2.652%

CI is one-sided, N = number, CI = credible interval

Success for this endpoint was achieved if the percentage of patients experiencing one of the events was statistically less than the performance goal, defined as 2.67%, with an upper bound of the one-sided 95% credible interval less than the performance goal.

There were six (6) events meeting the primary safety endpoint definition in 269 patients. Therefore, 2.2% of patients experienced an event and a one-sided 95% credible interval upper bound was 2.652%. Success of the primary safety endpoint was achieved.

Table 58 summarizes the types of primary safety endpoint events experienced during the study. This table is based upon event type for the first event noted in a patient.

Table 58: PREVAIL: Safety Primary Endpoint Events

Device Group		
Type	**N Events**	**% of Patients**
Device Embolization	2	0.7%
AV Fistula	1	0.4%
Cardiac Perforation	1	0.4%
Pericardial Effusion with Cardiac Tamponade	1	0.4%
Major Bleed Requiring Transfusion	1	0.4%

Types of events experienced were dispersed with no more than two events of any single type experienced.

9.5.4   Safety Summary

With prolonged follow-up in PROTECT AF, the rate ratio of a serious adverse event in the Device cohort was comparable to that of the Control Group. Additional safety data from the CAP Registry showed a decrease in procedure-related events. In PREVAIL, the study results met the pre-specified criterion for safety. The continuous improvement in the safety profile over the WATCHMAN clinical program is shown in Table 59.

Table 59: Decrease in Procedure-related Adverse Events over WATCHMAN Clinical Experience

Procedure-related Event	PROTECT AF	CAP Registry	PREVAIL
Ischemic stroke	5/449 (1.1%)	0/566 (0%)	1/265 (0.4%)
Cardiac perforation requiring surgical repair	7/449 (1.6%)	1/566 (0.2%)	1/265 (0.4%)
Pericardial tamponade requiring intervention	13/449 (2.9%)	7/566 (1.2%)	4/265 (1.5%)

The totality of the experience with the WATCHMAN Closure Device from the PROTECT AF, CAP, and PREVAIL studies support the conclusion that the device and its associated implant procedure are safe.

10 Additional Analyses

10.1 New and Experienced Operators - PREVAIL

The rate of procedural complications reported early in the PROTECT AF pivotal study was relatively high. It was found there was a procedural learning curve related to WATCHMAN device implantation, primarily with navigating the device into proper placement in the left atrial appendage. With physician experience and a modified training program the complication rate declined substantially. The PREVAIL study was designed to include investigational sites and operators with prior experience implanting the WATCHMAN device ("experienced") in the PROTECT AF or CAP Registry study, as well as sites and operators with no prior experience with the device ("new"). Utilizing new sites allowed for evaluation of efficacy of the physician training program and mitigation of procedural complications.

The protocol required a minimum randomized enrollment of 20% of patients by new sites and 25% of patients by new operators. New operators could participate at either new or experienced institutions. Additionally, new sites enrolled up to 2 Roll-in patients and experienced sites enrolled up to one Roll-in patient prior to randomization of patients.

10.1.1 Enrollment and Procedure Success by Operator/Site – New or Experienced

There were 41 participating sites in the PREVAIL study; of these, there were 23 (56%) experienced sites and 18 (44%) new sites. Table 60 shows the percentage of randomized patients enrolled in the study. There were 38.8% (158/407) randomized patients enrolled by new sites, surpassing the 20% protocol requirement; and 39.1% (159/407) randomized patients enrolled by new operators surpassing the 25% protocol requirement.

Table 60: PREVAIL: Experienced and New Enrollment

Category	Device Group	Control Group	Total Randomized
Site Type			
Experienced	165/269 (61.3%)	84/138 (60.9%)	249/407 (61.2%)
New	104/269 (38.7%)	54/138 (39.1%)	158/407 (38.8%)
Operator Type			
Experienced	164/269 (61.0%)	84/138 (60.9%)	248/407 (60.9%)
New	105/269 (39.0%)	54/138 (39.1%)	159/407 (39.1%)

Table 61 shows the overall PREVAIL enrollment summary and implant success by new and experienced operator. There were a total of fifty (50) operators in the study. Of these operators, 24/50 (48%), were new operators and 26/50 (52%) had prior WATCHMAN experience.

Of the 269 randomized device patients approximately 40% were enrolled by new operators. However, 63% (34/54) of the Roll-in patients were enrolled by new operators as they were allowed two Roll-in patients per protocol compared to enrollment of one Roll-in patient for experienced operators.

Table 61: PREVAIL: Experienced and New Enrollment Summary

Group	Experienced Operator	New Operator	Total N
WATCHMAN Device			
Randomized	164	105	269
Implant Attempt	162	103	265
Implanted	156	96	252
No Implant Attempt	2	2	4
Control Group			
Randomized	84	54	138
Roll-in			
Enrolled	20	34	54
Implant Attempt	20	34	54
Implanted	17	34	51

Implant success for experienced operators was 95% (173/182) for all patients and 96% (156/162) for randomized device patients. Implant success for new operators was 95% (130/137) for all patients and 93% (96/103) in randomized patients. Of note, new operators successfully implanted 100% of the Roll-in patients, their first implant attempts. These results demonstrate new operators have a similar implant success rate to operators with more substantial WATCHMAN implant experience.

The distribution of randomized device implantation was dispersed across all operators. On average new operators accounted for 5.7 (median 5.0) successfully implanted device patients. Experienced operators enrolled a mean of 6.9 (median 5.0) successfully implanted device patients.

10.1.2 *Primary Endpoints by Operator – New or Experienced*

In addition to implant success, the three primary endpoints for randomized device patients were evaluated according to operator experience to evaluate differences in safety or efficacy. This analysis was predefined in the statistical analysis plan.

The number of randomized device patients experiencing a first, second or third primary endpoint by type of operator are shown in Table 62.

Table 62: PREVAIL: Primary Endpoint by Operator Type – Randomized Device Patients Only

	New Operators		Experienced Operators	
	N Events/ N Patients	% of Patients	N Events/ N Patients	% of Patients
First Primary Endpoint (Composite efficacy)	2/105	1.9%	12/164	7.3%
Second Primary Endpoint (Late ischemic events)	0/105	0.0%	5/164	3.0%
Third Primary Endpoint (Acute safety)	2/105	1.9%	4/164	2.4%

There were similar rates of major procedural safety complications in the new and experienced operator subgroups. There were more first and second endpoint (efficacy) type events in the experienced operator group than in the new operator group, demonstrating that new operators do not impose a greater risk to patients than those operators with more experience. The higher rate of efficacy primary endpoint events experienced by patients of experienced operators may be due to a greater number of patients with a history of TIA/stroke (31.7%, 52/164 patients enrolled by experienced operators compared to 21.0%, 22/105 patients enrolled by new operators) and a slightly higher CHADS$_2$ score in patients enrolled by experienced operators compared to new operators, 2.6 and 2.4, respectively.

To assess whether or not there were differential event rates of the primary endpoints, evaluation of indicators for new versus experienced operators, site implant attempt number, and implant attempt date was performed. These analyses examined the role of a learning curve for the three primary endpoints within only the randomized device group. This analysis was pre-defined in the statistical analysis plan and the results are shown in Table 63.

Table 63: PREVAIL: Primary Endpoint Event Risk Models

Covariate	Efficacy Primary Endpoint		Mechanism of Action Primary Endpoint		Safety Primary Endpoint	
	Hazard Ratio (95% CI)	P-Value	Hazard Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value
New vs Experienced	0.29 (0.06, 1.30)	0.106	0.00 (0.00,)	0.995	0.78 (0.14, 4.32)	0.773
Site Implant Number	1.06 (0.97, 1.14)	0.199	0.89 (0.67, 1.17)	0.395	0.98 (0.85, 1.13)	0.776
Implant Attempt Date	1.00 (1.00, 1.01)	0.323	1.00 (1.00, 1.01)	0.377	1.00 (1.00, 1.00)	0.941

After the initiation of the present training program, there were no significant findings indicating a difference between new and experienced operators. A separate model was fit for each endpoint and covariate combination (for a total of nine separate models). For each, the risk of an endpoint event was assessed with a proportional hazards time to event model for the first two endpoints and a logistic regression model for the third endpoint. This approach facilitated the use of covariates for modeling as opposed to the Bayesian model for the primary endpoint that was designed for a comparison of the randomized groups for only the first two primary endpoints and similarly facilitated modeling for the third endpoint which is acute and not based on hazards over time.

For new versus experienced operators, a 1/0 indicator variable was used to compare new versus experienced operators. A hazard ratio or odds ratio less than 1 would indicate an decreased risk of an event for the new operators. The actual hazard ratios for the three primary endpoints were below 1, however, the p values were non-significant, demonstrating that new operators did not have a significant increase in primary endpoint events compared to experienced operators.

For site implant number and implant attempt date, each covariate was entered as a numerical variable so that the hazard or odds ratio compares each one unit increase in the covariate (a later implant number, a day later implant attempt). For example, for the first primary endpoint a later site implant number was associated with a non-significant increased hazards (hazard ratio 1.06). All findings for site implant number and implant attempt date were not significant for increased risk of endpoint occurrence.

Based on these results, Boston Scientific strongly believes in its training program for new implanters. An overview of the proposed post-approval training program may be found in Appendix G: Overview of Physician Training Program.

10.2 PROTECT AF, PREVAIL, and CAP Registry: Aggregate Primary Efficacy Analysis

Although Bayesian analyses were the pre-specified analysis for the PROTECT AF and PREVAIL studies, it may be interesting to take a purely descriptive approach without any Bayesian priors. This section provides a supplementary analysis that aggregated the individual patient data into a single set of Kaplan-Meier curves. As these trials were designed utilizing Bayesian methodologies, no predefined statistical conclusions should be drawn from this analysis, which is intended for illustrative purposes.

The CAP Registry, which was not randomized but used the same efficacy primary endpoint, is not aggregated with the two randomized studies and is also shown for illustrative purposes.

The upper left panel in Figure 25 depicts the efficacy primary endpoint for the PROTECT AF and PREVAIL WATCHMAN device arms and the CAP Registry results individually. The upper right panel in Figure 25 illustrates the warfarin control arms from the PROTECT AF and PREVAIL studies. The set of Kaplan-Meier curves in the lower center panel of Figure 25 shows the two Device Group arms combined and plotted against the two Control Group arms combined. The CAP Registry arm was not included in this final plot.

Figure 25: Aggregate of PROTECT AF and PREVAIL Studies with Reference to CAP Registry – Kaplan-Meier Curves
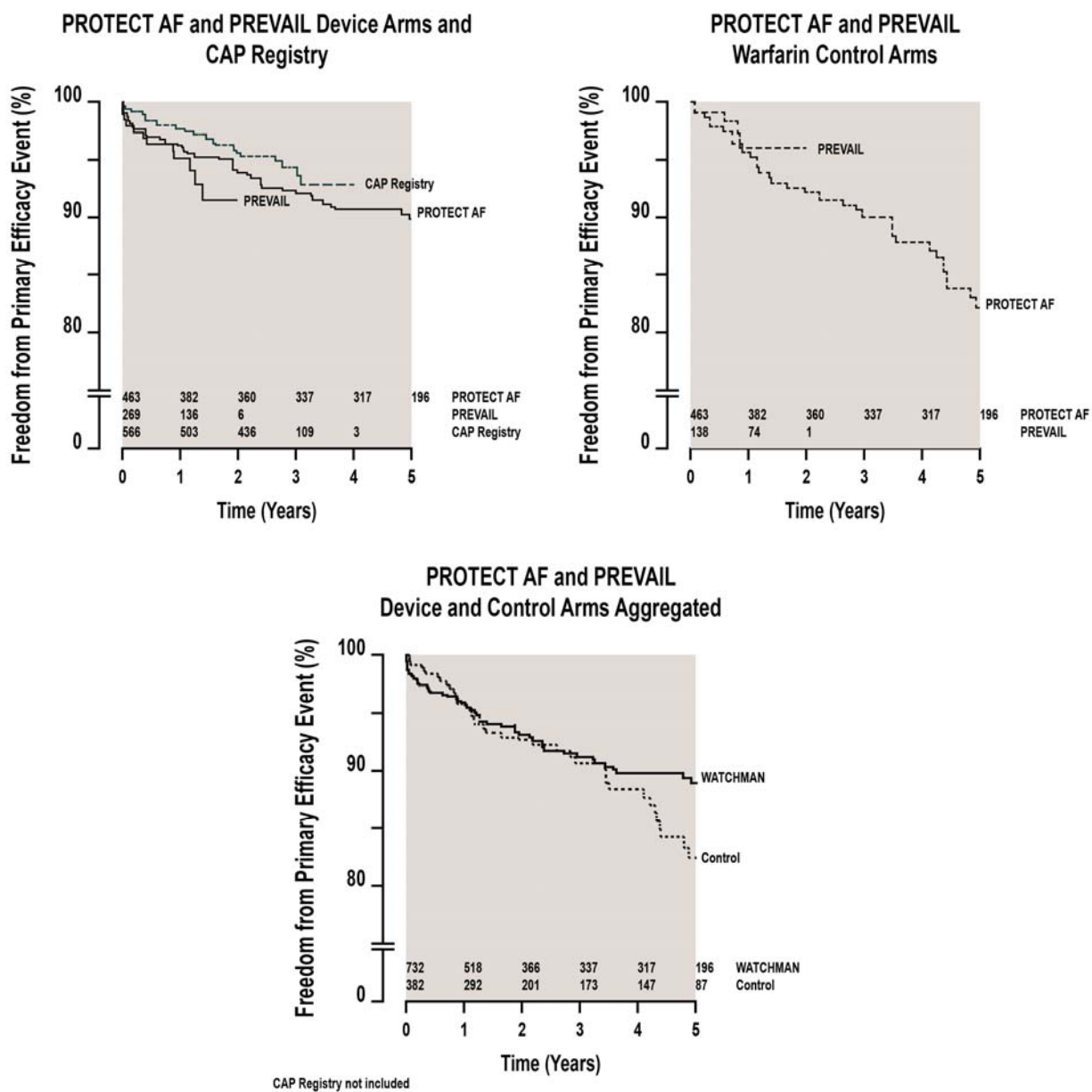
10.3 All-Cause Mortality: PROTECT AF and PREVAIL

10.3.1 PROTECT AF

Cardiovascular mortality was previously identified as a component of the PROTECT AF efficacy primary endpoint and examined and discussed in Section 9.4.2.2. All-cause mortality was also studied and is summarized in Table 64 and the time-to-event data plotted as a Kaplan-Meier curve in Figure 26.

Table 64: PROTECT AF: All-Cause Mortality

Device		Control			
Rate Per 100 Pt-yrs (N Events/Pt-yrs)	95% CrI for Rate	Rate Per 100 Pt-yrs (N Events/Pt-yrs)	95% CrI for Rate	Rate Ratio (95% CrI)	Posterior Probability
3.2 (57/1774.2)	2.5, 4.2	4.8 (44/919.5)	3.6, 6.4	0.67 (0.49, 1.08)	0.944

Figure 26: PROTECT AF: All-cause Mortality – Kaplan-Meier Curves
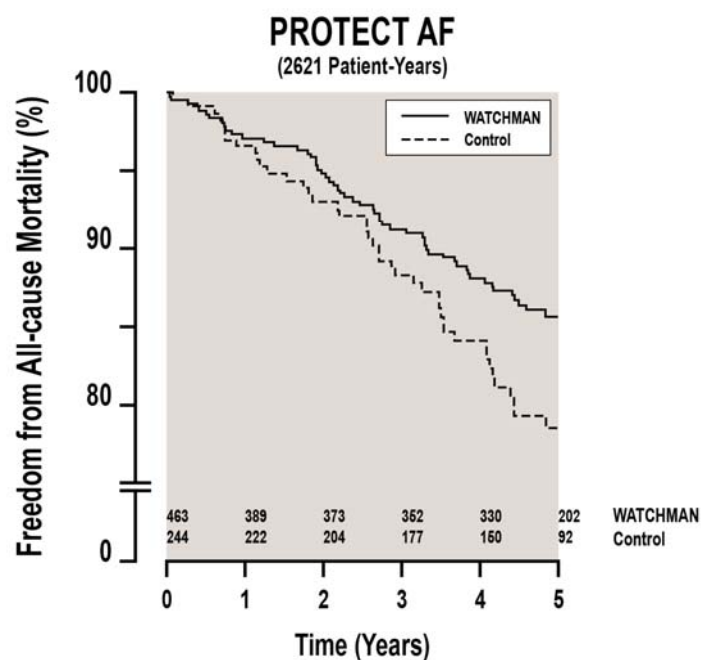
The cause of death was also examined by subcategory and is summarized in Table 65. A statistically significant difference favoring the WATCHMAN Closure device was detected in the category of cardiovascular death. Further examination of mechanisms of death within the cardiovascular subcategory revealed a statistically significant reduction in hemorrhagic stroke that was favorable to the WATCHMAN device. These analyses are post-hoc and should be interpreted with caution.

Table 65: PROTECT AF: Cause of Death

2:1 Randomization Device / Control

Category	Device N=463	Control N=244	P-value
Cancer	**10 (2.2%)**	**3 (1.2%)**	**0.56**
Cardiovascular	**17 (3.7%)**	**22 (9.0%)**	**0.0049**
Heart failure	3 (0.6%)	2 (0.8%)	1.00
Hemorrhagic stroke	2 (0.4%)	8 (3.3%)	0.0041
Ischemic stroke	1 (0.2%)	1 (0.4%)	1.00
Myocardial infarction	2 (0.4%)	2 (0.8%)	0.61
Sudden cardiac death	4 (0.9%)	4 (1.6%)	0.46
Unexplained/other	5 (1.0%)	5 (2.0%)	0.33
Multisystem Organ Failure	**6 (1.3%)**	**1 (0.4%)**	**0.43**
Neurologic	**2 (0.4%)**	**1 (0.4%)**	**1.00**
Pulmonary	**9 (1.9%)**	**9 (3.7%)**	**0.21**
Other	**9 (1.9%)**	**5 (2.0%)**	**1.00**
Renal Failure	3 (0.6%)	3 (1.2%)	0.42
Sepsis	2 (0.4%)	1 (0.4%)	1.00
Unexplained/Other	4 (0.9%)	1 (0.4%)	0.66

10.3.2 PREVAIL

Mortality rates were calculated for each randomized group. The time to death was calculated for each patient and those who had not expired were censored at the date of their last known vital status. Table 66 shows the all-cause mortality results for the randomized patients using the Bayesian model.

Table 66: PREVAIL: All-Cause Mortality Results

Device 18-Month Rate	Control 18-Month Rate	18-Month Rate Ratio (95% CrI)
0.028	0.045	0.67 (0.27, 1.41)

The 18-month rate in the Device Group was 0.028 compared to 0.045 in the Control Group. The 18-month rate ratio favored the Device Group and the 95% credible interval for the rate ratio was (0.27, 1.41). Applying the efficacy primary endpoint non-inferiority criteria, the Device Group was non-inferior to the Control Group.

The Kaplan-Meier analyses for freedom from all-cause mortality are shown in Figure 27.

Figure 27: PREVAIL: All-Cause Mortality - Kaplan-Meier Curves
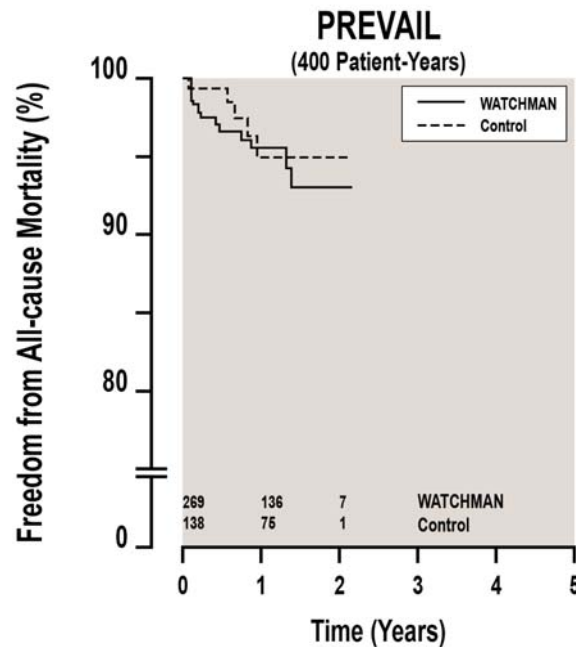
The pre-specified all-cause mortality analysis included all randomized patients in the group to which they were assigned. The following conclusions are made from the analysis:

- The 18-month rate of all-cause mortality in the Device Group was 0.028 compared to 0.045 in the Control Group. The 18-month rate ratio favored the Device Group and the 95% credible interval for the rate ratio was (0.27, 1.41).

- At 1 year, the Device Group had a Kaplan-Meier estimated all-cause mortality event rate of 4.7% compared to a 5.0% all-cause mortality event rate in the Control Group.

- None of the deaths in the Device Group were due to the device or implant procedure.

10.4   PROTECT AF: Disabling/Non-Disabling Strokes

Because not all safety events have the same clinical impact on the patient, a post-hoc analysis was conducted to determine the functional impact of being in either the WATCHMAN   or warfarin group in PROTECT AF. That is, the functional impact of the primary safety (including non–procedure- and device-related event) and efficacy events was assessed by determining whether they resulted in either significant disability (defined as an increase in the modified Rankin score [MRS]) or death. The modified Rankin score is a scale ranking the disability of a patient on a scale of 0-6, where 0 is perfect health and 6 is death.[27]

Not all strokes have the same impact on patients. Defining "disabling strokes" as those from 3-6 on the modified Rankin scale and "non-disabling strokes" as those from 0-2, it appears that non-disabling strokes occur at similar rates between the Device Group and the Control Group but that there are fewer disabling strokes in the Device group. The results suggest that over time the risk of a disabling stroke is less with the WATCHMAN device than with warfarin. This analysis was post-hoc and should be confirmed prospectively.

The results of this analysis are shown in relation to the components of the long-term PROTECT AF primary efficacy results by component in Table 67.

Table 67: PROTECT AF: Disabling and Non-Disabling Strokes between Groups

Analysis Cohort	WATCHMAN (n=463)	Control (n=244)	Rate Ratio (95% CrI)	Posterior Probabilities	
	Rate	Rate		Non-inferiority	Superiority
Primary Efficacy	2.3	3.8	0.60 (0.41, 1.05)	>0.999	0.960
Stroke (all)	1.5	2.2	0.68 (0.42, 1.37)	0.999	0.825
Ischemic	1.4	1.1	1.26 (0.72, 3.28)	0.779	0.147
Hemorrhagic	0.2	1.1	0.15 (0.03, 0.49)	0.999	0.999
Disabling	**0.5**	**1.2**	**0.37 (0.15, 1.00)**	**> 0.999**	**0.975**
Non-disabling	**1.0**	**1.0**	**1.05 (0.54, 2.80)**	**0.889**	**0.342**
Systemic embolism	0.2	0.0	NA	NA	NA
Death (CV & Unexplained)	1.0	2.4	0.40 (0.23, 0.82)	>0.999	0.995

10.5 Subgroup Analyses

10.5.1 PROTECT AF: Efficacy Primary Endpoint by Subgroup

An analysis of the efficacy primary endpoint was undertaken with the PROTECT AF data to assess whether certain subgroups had differential levels of success with the WATCHMAN device. No significant interactions were found between subgroups as shown in Figure 28.

Figure 28: PROTECT AF: Efficacy Primary Endpoint by Subgroup
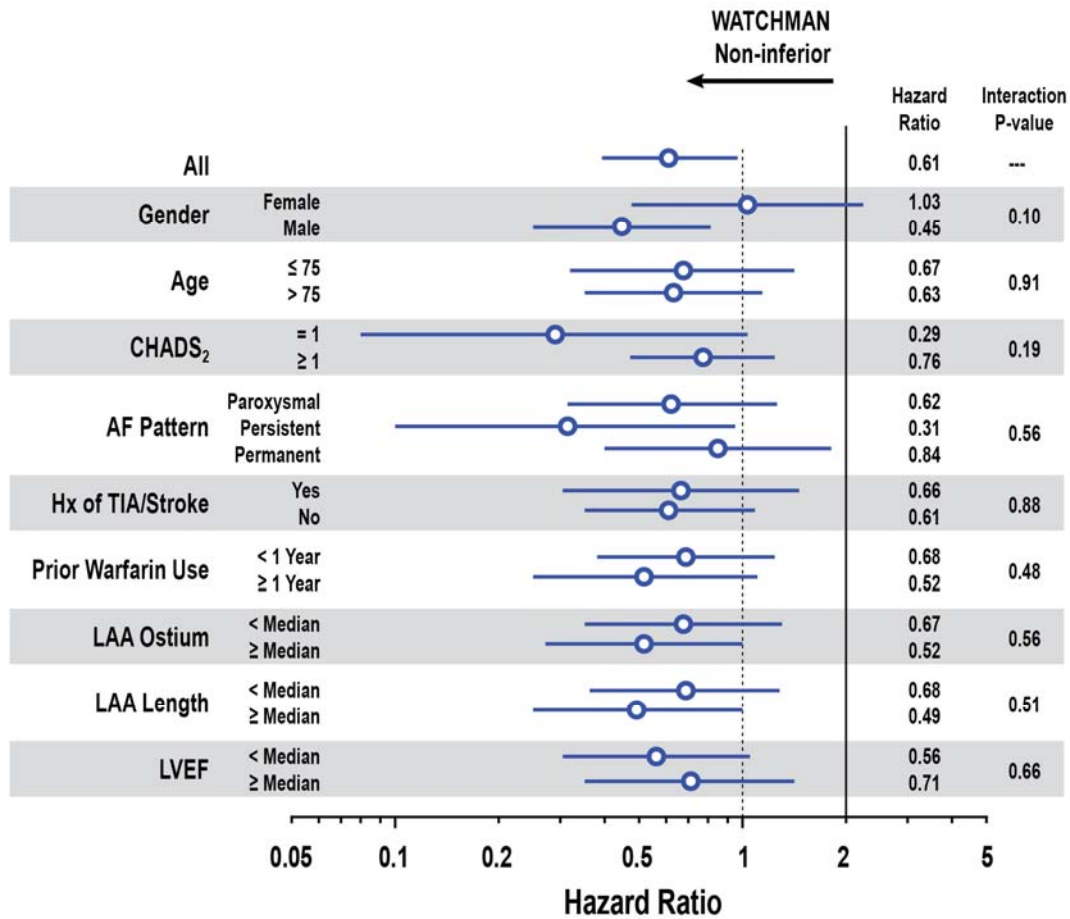
10.5.2 PREVAIL: Effects of Preoperative Characteristics on Primary Endpoints

In addition to the effect of investigational site on the primary endpoints, analyses for the effects of additional covariates were performed. The baseline covariates and their respective hazard ratios are shown in Table 68 for the efficacy primary endpoint.

Table 68: PREVAIL: Efficacy Primary Endpoint by Baseline Covariate

Covariate	Hazard Ratio (95% CI)	P-Value
Gender (Female vs. Male)	0.48 (0.14, 1.65)	0.2445
Age (Above vs. Below Median)	1.83 (0.71, 4.71)	0.2135
CHADS$_2$ Score (1-3 vs. 4-6)	0.28 (0.11, 0.72)	0.0079
AF Pattern (Non-Paroxysmal vs. Paroxysmal)	1.99 (0.74, 5.29)	0.1703
LVEF (Above vs. Below Median)	0.50 (0.19, 1.34)	0.1687
Device Size (21, 24mm vs. 27, 30, and 33mm)	0.99 (0.35, 2.82)	0.9820

These results demonstrate only the CHADS$_2$ score of 1-3 versus 4-6 has a statistically significant difference in the efficacy primary endpoint outcome, with a greater percentage of patients in the higher CHADS$_2$ subgroup (8.7%, 4/46) experiencing events than in the lower CHADS$_2$ subgroup (4.5%, 10/223).

To further compare the effects of the baseline covariates, an analysis of each covariate by randomized Device or Control Group was analyzed as summarized in Table 69.

Table 69: PREVAIL: Efficacy Primary Endpoint by Baseline Covariate and Randomization

Subgroup	Device % (n/N)	Control % (n/N)	Subgroup Hazard Ratio (95% CI)	Subgroup P-value	Interaction P-value
Gender					
Female	2.3% (2/87)	2.9% (1/35)	1.05 (0.09, 11.65)	0.967	0.490
Male	6.6% (12/182)	2.9% (3/103)	0.43 (0.12, 1.51)	0.187	
Age					
Above Median	7.2% (9/125)	3.1% (2/64)	0.38 (0.08, 1.76)	0.217	0.558
Below Median	3.5% (5/144)	2.7% (2/74)	0.75 (0.15, 3.87)	0.732	
CHADS$_2$ Category					
1-3	4.5% (10/223)	0.0% (0/110)	0.00	0.993	0.988
4-6	8.7% (4/46)	14.3% (4/28)	1.48 (0.37, 5.93)	0.584	
AF Pattern					
Other	6.5% (9/138)	4.5% (3/67)	0.63 (0.17, 2.31)	0.483	0.649
Paroxysmal	3.8% (5/131)	1.4% (1/71)	0.36 (0.04, 3.05)	0.346	
LVEF					
Above Median	2.3% (3/129)	4.2% (3/72)	1.70 (0.34, 8.40)	0.518	0.091
Below Median	7.9% (11/139)	1.5% (1/65)	0.18 (0.02, 1.39)	0.100	
Device Size (Device Group Only)					
21mm	7.7% (3/39)	.	.	.	.
24mm	4.8% (4/83)	.	.	.	.
27mm	4.8% (4/83)	.	.	.	.
30mm	5.4% (2/37)	.	.	.	.
33mm	10.0% (1/10)	.	.	.	.

Comparing baseline covariates by randomized groups demonstrates there were no statistically significant differences on the effect of the efficacy primary endpoint as shown in Table 68.

For the mechanism of action primary endpoint of late ischemic events, the effects of baseline covariates were analyzed and are shown in Table 70 and Table 71.

Table 70: PREVAIL: Mechanism of Action Primary Endpoint by Baseline Covariate and Randomization

Subgroup	Device % (n/N)	Control (n/N)	Subgroup Hazard Ratio (95% CI)	Subgroup P-value	Interaction P-value
Gender					
Female	1.1% (1/87)	2.9% (1/35)	1.96 (0.12, 31.53)	0.633	0.995
Male	2.2% (4/182)	0.0% (0/103)	N/A	0.995	
Age					
Above Median	3.2% (4/125)	1.6% (1/64)	0.41 (0.05, 3.67)	0.425	0.995
Below Median	0.7% (1/144)	0.0% (0/74)	N/A	0.998	
CHADS$_2$ Category					
1-3	0.9% (2/223)	0.0% (0/110)	N/A	0.997	0.995
4-6	6.5% (3/46)	3.6% (1/28)	0.45 (0.05, 4.35)	0.489	
AF Pattern					
Other	2.9% (4/138)	1.5% (1/67)	0.46 (0.05, 4.16)	0.493	0.995
Paroxysmal	0.8% (1/131)	0.0% (0/71)	N/A	0.998	
LVEF					
Above Median	0.8% (1/129)	1.4% (1/72)	1.68 (0.10, 26.83)	0.715	0.994
Below Median	2.9% (4/139)	0.0% (0/65)	N/A	0.995	
Device Size					
21	5.1% (2/39)	N/A	N/A		
24	2.4% (2/83)				
27	1.2% (1/83)				
30	0.0% (0/37)				
33	0.0% (0/10)				

Table 71: PREVAIL: Mechanism of Action Primary Endpoint by Baseline Covariate

Covariate	Hazard Ratio (95% CI)	P-Value
Gender (Female vs. Male)	1.18 (0.22, 6.45)	0.8470
Age (Above vs. Below Median)	5.80 (0.68, 49.66)	0.1086
CHADS$_2$ Score (1-3 vs. 4-6)	0.11 (0.02, 0.61)	0.0117
AF Pattern (Non-Paroxysmal vs. Paroxysmal)	4.98 (0.58, 42.65)	0.1426
LVEF (Above vs. Below Median)	0.50 (0.09, 2.75)	0.4287
Device Size (27, 30, and 33mm vs. 21, 24mm)	0.26 (0.03, 2.36)	0.2329

As with the efficacy primary endpoint, the CHADS$_2$ score was the only baseline covariate to have a statistically significant effect the mechanism of action primary endpoint.

The effect of baseline covariates on primary safety endpoint of acute procedural complications is shown in Table 72 for the randomized Device Group only.

Table 72: PREVAIL: Safety Primary Endpoint by Baseline Covariate

Subgroup	Device % (n/N)	Hazard Ratio (95% CI)	P-Value
Gender			
Female	3.4% (3/87)	2.12 (0.43, 10.49)	0.358
Male	1.6% (3/182)		
Age			
Above Median	2.4% (3/125)	1.15 (0.23, 5.70)	0.864
Below Median	2.1% (3/144)		
CHADS$_2$ Score			
1-3	2.7% (6/223)	444E4	0.994
4-6	0.0% (0/46)		
AF Pattern			
Other	2.9% (4/138)	1.90 (0.35, 10.37)	0.459
Paroxysmal	1.5% (2/131)		
LVEF			
Above Median	1.6% (2/129)	0.53 (0.10, 2.90)	0.464
Below Median	2.9% (4/139)		
Device Size			
21mm	0.0% (0/39)	0.00 (0.00,)	0.997
24mm	0.0% (0/83)	0.00 (0.00,)	0.996
27mm	3.6% (3/83)	0.34 (0.04, 3.24)	0.347
30mm	2.7% (1/37)	0.25 (0.02, 3.97)	0.325
33mm	10.0% (1/10)	.	.

There were no statistically significant differences on the effect of baseline covariates on the primary safety endpoint.

11 Post-approval Plans

Post-approval plans of the WATCHMAN Closure Device include implementation of a training program for new implants (see Appendix G: Overview of Physician Training Program), distribution of a patient guide (see Appendix H: Patient Guide), and conduct of a post-approval study of the WATCHMAN device (see Appendix I: Post-approval Study).

12 Conclusions

The totality of the data available with the WATCHMAN device from long-term results of the PROTECT AF study supplemented by the results of the CAP Registry and PREVAIL trial provides reasonable assurance of the safety and efficacy of the WATCHMAN LAAC Therapy to prevent embolism of thrombus from the left atrial appendage and thus reduce the risk of stroke, systemic embolism, and cardiovascular death in high risk patients with non-valvular atrial fibrillation who are eligible for warfarin therapy but for whom the risk posed by long term warfarin therapy outweigh the benefits.

12.1 Efficacy

The efficacy of the WATCHMAN Closure Device in preventing thromboembolic events and cardiovascular death has been demonstrated.

- ***Investigators were able to implant the device with a high degree of success***. Implant success rates have increased from 90.9% in PROTECT AF to 94.3% in the CAP Registry and 95.1% in PREVAIL.

- ***Patients were able to successfully cease the use of warfarin***. By 45 days, warfarin cessation occurred in at least 87% of patients successfully implanted with the device. This figure improved to at least 93% at one year.

- ***The PROTECT AF study met its efficacy primary endpoint of non-inferiority when comparing the WATCHMAN Closure Device to warfarin, eventually reaching superiority***. This endpoint was a composite of ischemic stroke, hemorrhagic stroke, systemic embolism, or death due to cardiovascular or unknown causes encompassing 2621 patient-years of follow-up. PROTECT AF demonstrated a 40% reduction in the risk of a primary endpoint event [rate ratio= 0.60, 95% CrI (0.41, 1.05), posterior probability >0.999 for non-inferiority, 0.960 for superiority].

- ***The PREVAIL study did not meet the efficacy primary endpoint***. This endpoint was the same as in PROTECT AF. The rate ratio was 1.07, CrI (0.57, 1.89) with a posterior probability of 0.958 for non-inferiority (posterior probability of 97.5% required to meet this endpoint).

- ***The WATCHMAN Closure Device is non-inferior to warfarin in reducing events due to ischemic stroke or systemic embolism (mechanism of action primary endpoint).*** In the PREVAIL study, the WATCHMAN Closure Device met its mechanism of action endpoint when compared to warfarin. The 18-month rate difference was 0.0053 with a

95% CrI of (-0.0190, 0.0273), which was within the non-inferiority margin of 0.0275 with a posterior probability of 0.978.

12.2 Safety

The safety of the WATCHMAN LAAC Therapy has been shown across the studies in the WATCHMAN clinical program.

- ***A substantial improvement in safety was seen early in the WATCHMAN clinical experience.*** The rate of safety events was reduced from the early PROTECT AF enrollment period to the late PROTECT AF enrollment period. Changes in training, the implant procedure, and technical aspects of the WATCHMAN device reduced the rate of safety events from 9.9% in the first half to 4.8% in the second half. The durability of this effect was evident in the CAP Registry in which the safety event rate was 4.1%.

- ***The safety endpoint in the PREVAIL study was met.*** The event rate was 2.2% with a 95% credible interval bound of 2.65%, within its pre-specified performance goal of 2.67%.

- ***Reductions in specific procedure-related events were observed over the progression of studies.*** From the PROTECT AF study through PREVAIL, the rates of cardiac perforations requiring surgery, pericardial effusion with tamponade, and procedure-related ischemic strokes declined. The rate of device embolization was small and consistent across the studies.

- ***The training program employed in PREVAIL was successful.*** The risk associated with the implant procedure was similar for both new and experienced operators.

Summary

The data available on the WATCHMAN device, from the initial PROTECT AF study, supplemented by the results of the CAP Registry and the PREVAIL trial consistently provides reasonable assurance of the safety and efficacy of the WATCHMAN LAAC Therapy

The WATCHMAN Closure Device can be safely implanted by trained operators to prevent embolism of thrombus from the left atrial appendage and reduce the risk of stroke, systemic embolism, and cardiovascular death in high risk patients. Between 87-96% of successfully implanted patients could discontinue the use of warfarin after 45 days. The primary efficacy endpoint was met in PROTECT AF and demonstrated superiority of the WATCHMAN device to warfarin. The totality of the data from these studies continues to support the findings that the WATCHMAN LAAC Therapy is safe and effective.

13 List of Appendices

Appendix A: Summary of WATCHMAN Studies

Appendix B: Directions for Use

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Appendix E: CEC Adverse Event Definitions

Appendix F: Single Center Violation of Good Clinical Practice and Sensitivity Analysis

Appendix G: Overview of Physician Training Program

Appendix H: Patient Guide

Appendix I: Post-approval Study

14 References

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Appendix A: Summary of WATCHMAN Studies

Four additional clinical studies have been conducted on the WATCHMAN device as follows (in order of relevance):

Study	Enrollment Completion	Study Type and Objective
CAP	June 30, 2010	Continued Access Registry: continued availability to US population
PILOT	January 26, 2005	Feasibility Study: first use of product and discovered concerns that lead to major design changes
ASAP	November 22, 2011	Feasibility Study: related population contraindicated to warfarin therapy
CAP2	Currently enrolling	Continued Access Registry: continued availability to US population

Continued Access to PROTECT AF Registry (CAP Registry)

Primary Objective: Demonstrate that the WATCHMAN LAAC Therapy is safe and effective in subjects with non-valvular atrial fibrillation who are eligible for warfarin therapy to prevent potential thrombus formation.

Design: The CAP Registry was a multi-center prospective non-randomized design allowing continued access to the WATCHMAN device during the preparation and evaluation of the first PMA for the WATCHMAN device. Up to 30 investigative centers with prior WATCHMAN experience in the PROTECT AF study were allowed to participate and enroll a maximum of 750 subjects. Study participants were required to be at least 18 years of age with non-valvular atrial fibrillation who are eligible for long-term warfarin therapy. Following baseline evaluation and device implant, subjects were seen at 45 days, 6, 9, and 12 months and semi-annually thereafter through 5 years.

The CAP registry evaluated endpoints identical to those used in the PROTECT AF study although there was no pre-defined hypothesis. The primary effectiveness endpoint was the successful treatment of subjects without stroke (including ischemic and hemorrhagic), cardiovascular death (cardiovascular and unexplained) and systemic embolism. The primary safety endpoint was treatment of the subject without the occurrence of life-threatening events as determined by the Clinical Events Committee (CEC), which would include events such as device embolization requiring retrieval, bleeding events such as pericardial effusion requiring drainage, cranial bleeding events due to any source, gastrointestinal bleeding requiring transfusion and any bleeding related to the device or procedure that necessitated a surgical procedure.

Demographics: A total of 26 centers (24 U.S., 2 European) actively participated by enrolling at least one subject in the study. A total of 566 subjects were enrolled. The average CHADS$_2$ score was 2.5 ± 1.2, the mean age was 74 years, and 66% of subjects were male. The mean follow-up of subjects was 29 months.

Summary of Results: The WATCHMAN device was successfully implanted in 534/566 (94%) subjects. For the primary efficacy endpoint, a rate of 2.0 events/100 patient-years was observed, with ischemic stroke being the most common event over a mean follow-up duration of 29 months. The data showed decreases in rates of pericardial effusion with tamponade, cardiac perforation, procedural strokes, and device embolization when compared to the PROTECT AF study. There were no procedure-related strokes or deaths during implant of the device with no long-term device migrations or erosions. In addition, 96% of subjects were able to discontinue warfarin therapy by 12 months. The results of this study helped confirm the findings observed in PROTECT AF.

Research Study of the WATCHMAN Left Atrial Appendage Filter System (PILOT)

Primary Objective: Evaluate the safety of the WATCHMAN device in subjects with non-valvular atrial fibrillation who required treatment for potential thrombus formation and were eligible for warfarin therapy.

Design: The study was a one-armed feasibility study intended to document Major Adverse Events (MAEs) specific to the study, which included ischemic stroke, systemic embolism, major bleeding and death as well as complications associated with the WATCHMAN device, both during the procedure and follow-up. Main entry criteria included, but were not limited to, age 18 or older, chronic or paroxysmal AF requiring treatment for potential thrombus formation and eligible for warfarin therapy. Pre-implant, subjects were evaluated with transesophageal echo (TEE) to rule out thrombus. After undergoing the implant procedure, patients were followed at 45 days, 6 months, 12 months, and annually thereafter. Repeat TEE were performed at 45 days and 6 months to verify device position and assess LAA closure.

Demographics: The average $CHADS_2$ in this population was 1.8 ± 1.1. The average age was 69 ± 8 years and the population was 34% female and 100% Caucasian.

Summary of Results: The WATCHMAN device was successfully implanted in 66/75 (88%) subjects, with discontinuation of warfarin in 68% at 45 days, 92% by six months, and 96% by 60 months. Mean follow-up in this study was 6.1 years. There were no deaths, no device embolizations related to the Gen 2.0/2.5 device, and no evidence of long-term erosion. These results supported progression to a pivotal study.

ASA Plavix Feasibility Study with WATCHMAN Left Atrial Appendage Closure Technology (ASAP Study)

Primary Objective: Characterize the performance of the WATCHMAN device in non-valvular atrial fibrillation (AF) subjects with <u>contraindications</u> to warfarin therapy. Subjects were prescribed aspirin and clopidogrel therapy post implant for 6 months rather than the usual six weeks of warfarin therapy.

Design: The study was a multicenter, prospective, non-randomized feasibility study of the WATCHMAN device in warfarin contraindicated subjects conducted at four investigational centers in Europe. In addition to a contraindication for warfarin, study participants were required to be at least 18 years of age and have recurrent non-valvular atrial fibrillation with a $CHADS_2$ score of 1 or greater, and an LVEF at least 30% or greater. Subjects were followed at 3, 6, 12, 18, and 24 months with TEE examinations at 3 and 12 months to assess the WATCHMAN device. This study did not have formal hypothesis testing but instead used descriptive statistics to characterize event rates for all-cause mortality, ischemic and hemorrhagic stroke, and device thrombus as well as serious procedure or device-related adverse events.

Demographics: The average $CHADS_2$ in this population was 2.8±1.2. The average age was 73±7 years and the population was 36% female. The most common contraindication to warfarin therapy was a history of bleeding tendencies (67%).

Summary of Results: The WATCHMAN device was successfully implanted in 142/150 (95%) subjects with a mean follow-up duration of 17 months. The deaths were adjudicated by an external Clinical Events Committee (CEC) and considered to not be device related. Detailed information is located in the ASAP Clinical Study Report. There was no evidence of long-term erosion. Event rates observed in the study are summarized in **Table 1**.

Table 1: ASAP Event rates

Event	Events/Pt-yrs (Rate per 100 Pt-yrs)
Death (All-Cause)	11/213.7 (5.1)
Stroke	5/209.0 (2.4)
Stroke - Ischemic	4/210.4 (1.9)
Stroke - Hemorrhagic	1/212.3 (0.5)
Device Thrombus	8/205.4 (3.9)

Ischemic stroke was reported in four (4) subjects for a rate of 1.9 per 100 pt-yrs. This rate is significantly lower than other trials assessing stroke rates in subjects with atrial fibrillation who are unable to take anticoagulant therapy. All stroke and ischemic stroke rates in ASAP were similar to those observed in the randomized non-inferiority PROTECT AF study despite having a higher $CHADS_2$ stroke risk. These results suggest that it may be safe to implant the WATCHMAN device in patients with contraindications to warfarin therapy.

Continued Access to PREVAIL Registry (CAP2)

Primary Objective: Demonstrate that the WATCHMAN LAAC Therapy is safe and effective in subjects with non-valvular atrial fibrillation who are eligible for warfarin therapy to prevent potential thrombus formation.

Design: The CAP2 Registry is a multi-center prospective non-randomized design allowing continued access to the WATCHMAN device during the preparation and evaluation of this PMA for the WATCHMAN device. Up to 60 investigative centers with prior WATCHMAN experience are allowed to participate and enroll an initial cohort of 300, up to a maximum of 1500 subjects. Study participants are required to be at least 18 years of age with non-valvular atrial fibrillation who are eligible for long-term warfarin therapy. Following baseline evaluation and device implant, subjects will be seen at 45 days, 6 and 12 months and semi-annually through 3 years, and annually thereafter through 5 years.

Descriptive statistics will be used for baseline, procedure and follow-up data collected through the study. Analyses may include, but will not be limited to, the following: procedural success, procedural complications, and incidence of stroke leading to significant disability/death. Any adverse events associated with screened failures who have diagnostic testing to assess eligibility for the device or for device implantation, or who have medication changes in preparation for device implantation will be included in the analyses.

Enrollment started September 25, 2012, and enrollment is ongoing. Subjects will be followed through their 5 year follow-up visit.

Appendix B: Directions for Use

The subsequent pages contain the WATCHMAN Access System Directions for Use and the WATCHMAN Left Atrial Appendage Closure Device with Delivery System Directions for Use.

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WATCHMAN®
Access System

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Access Sheath with Dilator

TABLE OF CONTENTS

℞ ONLY

Caution: Federal Law (USA) restricts this device to sale by or on the order of a physician.

WARNING

Contents supplied STERILE using an ethylene oxide (EO) process. Do not use if sterile barrier is damaged. If damage is found, call your Boston Scientific representative.

For single use only. Do not reuse, reprocess or resterilize. Reuse, reprocessing or resterilization may compromise the structural integrity of the device and/or lead to device failure which, in turn, may result in patient injury, illness or death. Reuse, reprocessing or resterilization may also create a risk of contamination of the device and/or cause patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness or death of the patient.

After use, dispose of product and packaging in accordance with hospital, administrative and/or local government policy.

DEVICE DESCRIPTION

The WATCHMAN Access System (Access Sheath and Dilator) is compatible with components of the WATCHMAN Left Atrial Appendage Closure Device.

Contents

Quantity	Description
1	WATCHMAN Access System

INTENDED USE/ INDICATIONS FOR USE

The WATCHMAN Access System is intended to provide vascular and transseptal access for the WATCHMAN Left Atrial Appendage Closure Device with Delivery System.

CONTRAINDICATIONS

Refer to WATCHMAN Left Atrial Appendage Closure Device with Delivery System DFU.

WARNINGS

Refer to WATCHMAN Left Atrial Appendage Closure Device with Delivery System DFU.

PRECAUTIONS

Refer to WATCHMAN Left Atrial Appendage Closure Device with Delivery System DFU.

HOW SUPPLIED

Do not use if package is opened or damaged.

Do not use if labeling is incomplete or illegible.

Handling and Storage

Store in a cool, dry, dark place.

PROCEDURAL INSTRUCTIONS

1. Use standard practice to puncture vessel and insert 0.035″ guidewire and vessel dilator. Use a standard transseptal access system to cross inter-atrial septum.

2. Exchange crossing sheath with exchange length extra support 0.035″ guidewire. Position guidewire in left upper pulmonary vein (LUPV) or loop in left atrium.

3. Prepare WATCHMAN Access System.

    A. Remove Access Sheath and Dilator under sterile conditions.

    B. Inspect prior to use to ensure no damage. Inspect sterile package and WATCHMAN Access System prior to use. If sterile barrier has been compromised in any way, DO NOT USE.

    C. Flush Access Sheath and Dilator with sterile saline prior to use.

    D. Insert Dilator into hemostasis valve of Access Sheath.

4. Advance WATCHMAN Access System over guidewire into left atrium (LA). As Access Sheath nears center of LA, hold Dilator and advance Access Sheath into initial position in LA or ostium of LUPV.

> **PRECAUTION:** Use caution when introducing WATCHMAN Access System to prevent damage to cardiac structures.

5. Remove Dilator and guidewire, leaving Access Sheath. Allow back bleed to minimize potential for introducing air before tightening valve. Flush with saline.

6. Confirm LAA size and select appropriate WATCHMAN LAA Closure Device.

    A. Using TEE, measure LAA ostium width and LAA length in 3-4 views (0°, 45°, 90°, 135°).

    B. Record multiple angles on cine with contrast prior to advancing Access Sheath into LAA. Use fluoro guidance while advancing pigtail catheter, or Access Sheath. Stop if resistance is felt.

    C. Choose a device based on **maximum** LAA ostium width recorded. Use Table 1 as a guide.

    > **NOTE:** LAA anatomy should accommodate a Device as described in Table 1.

TABLE 1. WATCHMAN LAA Closure Device Selection

Max LAA Ostium (mm)	Device Diameter (mm)
17 – 19	21
20 – 22	24
23 – 25	27
26 – 28	30
29 – 31	33

D. Carefully advance pigtail catheter through Access Sheath into distal LAA under fluoro guidance. Carefully advance Access Sheath over pigtail catheter until Access Sheath marker band corresponding to Device size (see Figure 1) is at or just distal to LAA ostium. Slowly remove pigtail catheter.
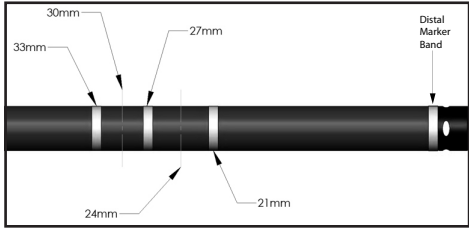
Figure 1. WATCHMAN® Access Sheath Marker Bands

WARRANTY

Boston Scientific Corporation (BSC) warrants that reasonable care has been used in the design and manufacture of this instrument. **This warranty is in lieu of and excludes all other warranties not expressly set forth herein, whether express or implied by operation of law or otherwise, including, but not limited to, any implied warranties of merchantability or fitness for a particular purpose.** Handling, storage, cleaning and sterilization of this instrument as well as other factors relating to the patient, diagnosis, treatment, surgical procedures and other matters beyond BSC's control directly affect the instrument and the results obtained from its use. BSC's obligation under this warranty is limited to the repair or replacement of this instrument and BSC shall not be liable for any incidental or consequential loss, damage or expense directly or indirectly arising from the use of this instrument. BSC neither assumes, nor authorizes any other person to assume for it, any other or additional liability or responsibility in connection with this instrument. **BSC assumes no liability with respect to instruments reused, reprocessed or resterilized and makes no warranties, express or implied, including but not limited to merchantability or fitness for a particular purpose, with respect to such instruments.**

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Recyclable Package

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WATCHMAN®

1 2 F

Left Atrial Appendage Closure Device with Delivery System

℞ ONLY

Caution: Federal Law (USA) restricts this device to sale by or on the order of a physician.

WARNING

Contents supplied STERILE using an ethylene oxide (EO) process. Do not use if sterile barrier is damaged. If damage is found, call your Boston Scientific representative.

For single use only. Do not reuse, reprocess or resterilize. Reuse, reprocessing or resterilization may compromise the structural integrity of the device and/or lead to device failure which, in turn, may result in patient injury, illness or death. Reuse, reprocessing or resterilization may also create a risk of contamination of the device and/or cause patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness or death of the patient.

After use, dispose of product and packaging in accordance with hospital, administrative and/or local government policy.

DEVICE DESCRIPTION

The WATCHMAN Left Atrial Appendage Closure (LAAC) Therapy consists of the Access System (Access Sheath and Dilator) and Delivery System [Delivery Catheter and Left Atrial Appendage (LAA) Closure Device]. The Access System and Delivery System permit Device placement in the LAA via femoral venous access and inter-atrial septum crossing into the left atrium. The WATCHMAN Device is a self-expanding nitinol structure with a porous membrane on the proximal face. The Device is constrained within the Delivery System until deployment in the LAA. The Device is available in 5 sizes from 21 to 33 mm. Device selection is determined by LAA measurements using Fluoroscopy (Fluoro) and Transesophageal Echocardiography (TEE).

The WATCHMAN LAA Closure Device is designed to be permanently implanted at or slightly distal to the ostium (opening) of the LAA to trap potential emboli before they exit the LAA. The

placement procedure can be done under local or general anesthesia in a catheterization laboratory setting.

Contents

Quantity	Description
1	WATCHMAN Left Atrial Appendage Closure Device with Delivery System

INTENDED USE

The WATCHMAN is a percutaneous, transcatheter closure device intended for non-surgical closure of the left atrial appendage.

INDICATIONS FOR USE

The WATCHMAN LAAC Therapy is intended to prevent embolism of thrombus from the left atrial appendage and thus reduce the risk of stroke, systemic embolism, and cardiovascular death in high-risk patients with non-valvular atrial fibrillation who are eligible for warfarin therapy but for whom the risk posed by long-term warfarin therapy outweigh the benefits.

CONTRAINDICATIONS

Do not use the WATCHMAN LAA Closure Device if:

- Intracardiac thrombus is visualized by echocardiographic imaging.
- An atrial septal repair or closure device is present.
- The LAA anatomy will not accommodate a Device. See **Table 8**.
- Any of the customary contraindications for other percutaneous catheterization interventions e.g. patient size (i.e. too small for TEE probe, catheter size, etc.) or condition (i.e. active infection, bleeding disorder, untreated ulcer, etc.) are present.

WARNINGS

Implantation of the WATCHMAN LAA Closure Device should only be performed by physicians trained in percutaneous and transseptal procedures who have completed the WATCHMAN training program.

- The LAA is a thin walled structure. Use caution when accessing the LAA and deploying the device.
- The WATCHMAN Access and Delivery Systems are sterile and intended for single use only. Do not reuse or resterilize. Reuse

could result in product damage and/or breakage that could lead to clinical complications, possibly requiring prolonged hospitalization. Resterilization could result in product contamination resulting in infection (e.g. endocarditis/ sepsis/local infection), possibly requiring antibiotics or prolonged hospitalization.

- Device selection should be based on accurate LAA measurements obtained using Fluoro and TEE in multiple angles (e.g. 0º, 45º, 90º, 135º).
- Aspirin should be started one day prior to scheduled procedure and continued daily.
- Patients should be fully heparinized throughout the procedure with an activated clotting time (ACT) of 200 - 300 seconds after transseptal puncture.
- Fluoro and TEE should be used when implanting the Device.
- Do not release (unscrew) the Device unless release criteria (step 14) are satisfied.
- Potential for Device embolization exists with cardioversion < 30 days following Device implantation, verify Device position post cardioversion.
- Post-procedure warfarin therapy is required in ALL patients receiving a Device who are eligible for warfarin therapy or other equivalent oral anticoagulant per institution's protocol. Patients should remain on 81-100 mg of aspirin and warfarin for a minimum of 45 days post implant (INR 2.0-3.0). At 45 days post implant perform Device assessment with TEE. Cessation of warfarin is at physician discretion. Patients ceasing warfarin should begin clopidogrel 75 mg daily and increase aspirin dosage to 300-325 mg daily for 6 months post-implant and remain on aspirin 300-325 mg indefinitely.
- Administer appropriate endocarditis prophylaxis for 6 months following device implantation. The decision to continue endocarditis prophylaxis beyond 6 months is at physician discretion.
- Do not release the WATCHMAN Device from the core wire if the Device does not meet release criteria (Step 14).

PRECAUTIONS

- Use caution when introducing WATCHMAN Access System to prevent damage to cardiac structures.
- Use caution when introducing Delivery System to prevent damage to cardiac structures.
- Do not allow WATCHMAN® Device to protrude to prevent damage to Delivery System.
- If using a power injector, the maximum pressure **should not** exceed 100 psi.

MAGNETIC RESONANCE IMAGING

Non-clinical testing has demonstrated that the WATCHMAN LAA Closure Device is MR Conditional. A patient with the Device can be scanned safely, immediately after placement of this implant, under the following conditions:

- Static magnetic fields of 3.0 Tesla or 1.5 Tesla
- Spatial gradient field of 2500 Gauss/cm or less
- The maximum whole body averaged specific absorption rate (SAR) shall be limited to 2.0 W/kg (normal operating mode only) for 15 minutes of scanning.
- Normal operating mode of the MRI scanner

The WATCHMAN LAA Closure Device should not migrate in this MRI environment. MR imaging within these conditions may be performed immediately following the implantation of the device. This device has not been evaluated to determine if it is MR Conditional beyond these parameters.

3.0 Tesla Temperature Information

In non-clinical testing, the WATCHMAN LAA Closure Device produced a temperature rise of < 1.1°C at a maximum MR system-reported SAR of 2.0 W/kg as measured by calorimetry for 15 minutes of continuous MR scanning in a 3.0 Tesla MR system (Excite, Software G3.0-052B, GE Healthcare, Milwaukee, WI).

These calculations do not take into consideration the cooling effects of blood flow.

1.5 Tesla Temperature Information

Non-clinical testing of RF-induced heating in the WATCHMAN LAA Closure Device was performed at 64 MHz in a 1.5 Tesla whole body coil MR scanner (Intera, Software Release 10.6.2.4, 2006-03-10, Philips Medical Systems, Andover, MA) and produced a temperature rise of < 1.5°C at an MR extrapolated SAR of 2.0 W/kg for 15 minutes of continuous MR scanning.

These calculations do not take into consideration the cooling effects of blood flow.

Image Artifact Information

MR image quality may be compromised if the area of interest is relatively close to the WATCHMAN device. Optimization of MR imaging parameters is recommended.

SUMMARY OF PRIMARY CLINICAL STUDIES

The WATCHMAN Left Atrial Appendage Closure (LAAC) device was evaluated for permanent implant to prevent thrombus embolization from the left atrial appendage in subjects with non-valvular atrial fibrillation in subjects who are eligible for warfarin therapy. The first human feasibility clinical study commenced in 2002 (PILOT), and then proceeded to the pivotal WATCHMAN LAAC Therapy for Embolic PROTECTion in Patients with Atrial Fibrillation (PROTECT AF) study. Two additional studies followed PROTECT AF in this population: a continued access (CAP) registry of the PROTECT AF study, and a second pivotal study, the Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy (PREVAIL) study. These four studies enrolled subjects that were able to tolerate long-term warfarin therapy as warfarin was used in the post-procedure period during endothelialization of the device. A fifth study, the ASA Plavix Feasibility Study (ASAP), was conducted to assess device performance in a similar population who were *contraindicated* for warfarin therapy. This overview includes a summary of each of the study designs, as well as results from each study. A summary of each study design is presented in **Table 1**.

PILOT Study

The PILOT Study was a prospective, non-randomized feasibility study conducted to evaluate the safety of the WATCHMAN device in subjects with non-valvular atrial fibrillation who required treatment for potential thrombus formation and were eligible for warfarin therapy. This study did not include a formal hypothesis, but a statistical summary of Major Adverse Events (MAEs) was used to evaluate safety. The definition of MAE included ischemic stroke, systemic embolism, major bleeding and death as well as complications associated with the WATCHMAN device, both during the procedure and follow-up. A total of 84 subjects were enrolled at 11 worldwide investigational

centers. Of these, 75 underwent an implant attempt and 66 were successfully implanted with a WATCHMAN device. Of the 66 implanted subjects, 16 received the Generation 1 device, 23 received the Generation 2 device, and 27 received Generation 2.5 device (device used in all subsequent studies). The PILOT study was conducted at approved investigational sites in both Europe and the United States with active enrollment phase from August 2002 to January 2005 in Europe, and October 2003 to January 2005 in the U.S. European centers followed subjects long term until the sponsor ended the follow-up phase in September 2011. Study centers in the U.S. completed five years of subject follow-up, per U.S. protocol, and were closed in 2010.

PROTECT AF Study

The PROTECT AF study was a multicenter, prospective randomized study comparing the WATCHMAN device to a control (long-term warfarin therapy). The purpose of the study was to demonstrate that the WATCHMAN LAAC Therapy is safe and effective in subjects with non-valvular atrial fibrillation who were eligible for anticoagulation therapy for potential thrombus formation. A 2:1 randomization allocation ratio was used with stratification by center such that for every one subject randomized to the Control arm (long-term warfarin therapy), two subjects were randomized to the Device arm to receive the WATCHMAN device.

The primary efficacy endpoint was the successful treatment without stroke (including ischemic and hemorrhagic), cardiovascular death (cardiovascular and unexplained) and systemic embolism. The primary statistical objective was to determine if the Device group is non-inferior to the Control group with respect to the event rate for the composite primary efficacy endpoint.

A total of 800 subjects were enrolled in the study at 59 centers. A 2:1 randomization allocation ratio was implemented across investigational centers in the randomized cohort. The 800 subjects included 463 subjects randomized to the Device group, 244 subjects randomized to the Control group and 93 Roll-in subjects.

CAP Registry

The CAP Registry was a multi-center prospective non-randomized design allowing continued access to the WATCHMAN Device during regulatory review of the post-market application for the WATCHMAN device. Entry criteria remained the same as the PROTECT AF study. A total of 26 centers (24 U.S., 2 European) actively participated by enrolling at least one subject in the study. A total of 566 subjects were enrolled from August 2008 through June 2010.

While no formal hypothesis testing was pre-defined, descriptive statistics were evaluated for the same primary efficacy and safety endpoints defined in PROTECT AF. The primary efficacy endpoint was evaluation of the composite of stroke (including ischemic and hemorrhagic), cardiovascular death (cardiovascular and unexplained) and systemic embolism. The primary safety endpoint was treatment of the subject without the occurrence of life-threatening events as determined by the Clinical Events Committee, which included events such as device embolization requiring retrieval, bleeding events such as pericardial effusion requiring drainage, cranial bleeding events due to any source, gastrointestinal bleeds requiring transfusion and any bleeding related to the device or procedure that necessitate an operation.

PREVAIL Study

The PREVAIL study was a multicenter, prospective randomized study to evaluate the safety and effectiveness of the WATCHMAN device compared to control (long-term warfarin therapy). This was the second pivotal, randomized study of the WATCHMAN device which was conducted to demonstrate the safety and efficacy results observed in the PROTECT AF study. There were three primary endpoints (two efficacy and one safety) as follows: 1) Composite of ischemic stroke, hemorrhagic stroke, systemic embolism, and cardiovascular/explained death, 2) Ischemic stroke and systemic embolism, excluding events occurring in the first 7 days following randomization and 3) Occurrence of all-cause mortality, ischemic stroke, systemic embolism, or device or procedure related events requiring open cardiac surgery or major endovascular intervention between the time of randomization and 7 days of the procedure or by hospital discharge, whichever is later. A total of 461 subjects at 41 U.S. investigational sites were enrolled from November 2010 through June 2012.

ASAP Study

The ASA Plavix Feasibility study with WATCHMAN LAAC Therapy (ASAP) study was a multi-center, prospective non-randomized study. The primary objective of the study was to characterize the performance of the WATCHMAN device in non-valvular atrial fibrillation subjects for whom warfarin therapy was contraindicated. Since ASAP was designed as a feasibility study, there was no formal hypothesis testing. Events of clinical interest, which included death, stroke (ischemic and hemorrhagic), device thrombus, and adverse events were recorded and summarized with descriptive statistics. One hundred fifty (150) subjects at four sites in Europe participated in the study. Enrollment commenced in January 2009 and concluded in November 2011.

Table 1. Summary of WATCHMAN Clinical Studies

Patient Population	Subjects with non-valvular atrial fibrillation who:				
	Eligible for warfarin therapy to prevent thrombus formation				Contraindicated for warfarin
Study	**PILOT**	**PROTECT AF**	**CAP**	**PREVAIL**	**ASAP**
Purpose	Demonstrate feasibility of WATCHMAN device implant	Demonstrate safety and efficacy compared to long-term warfarin	Demonstrate safety and efficacy	Demonstrate safety and efficacy compared to long-term warfarin	Demonstrate feasibility of WATCHMAN in subjects contraindicated to warfarin
Study Design	Non-randomized	Randomized, non-inferiority	Non-randomized	Randomized, non-inferiority	Non-randomized
Primary Endpoint	Major adverse events	Stroke, cardiovascular death, and systemic embolism		1. Stroke, systemic embolism, and cardiovascular/unexplained death 2. Ischemic stroke or systemic embolism occurring after seven days 3. Seven-day occurrence of death, schemic stroke, systemic embolism and procedure/device-related complications	Stroke, cardiovascular death, and systemic embolism
Number of Patients Enrolled	84	800 enrolled (707 randomized / 93 roll-in subjects)	566	461 (407 randomized / 54 roll-in subjects)	150
Follow-Up Duration	U.S.: 5 years OUS: 9 years	5 years		5 years	2 years

ADVERSE EVENTS

Observed Adverse Events

Observed adverse event experience comes from the PILOT, PROTECT AF, CAP, ASAP, and PREVAIL studies. Major clinical events for these studies are shown in **Table 2**.

Table 2. PILOT, PROTECT AF, CAP, ASAP, and PREVAIL Major Clinical Events

Event	PILOT N (%)	PROTECT AF N (%)	CAP N (%)	ASAP N (%)	PREVAIL N (%)
Pericardial effusion with cardiac tamponade	2 (2.7)	13 (2.8)	7 (1.2)	2 (1.3)	4 (1.5)
Pseudoaneurysm	4 (5.3)	3 (0.6)	5 (0.9)	1 (0.7)	-
Device embolization	3 (4.0)	3 (0.6)	1 (0.2)	2 (1.3)	2 (0.7)
Stroke – ischemic	1 (1.3)	7 (1.5)	-	1 (0.7)	1 (0.4)
Pericardial effusion-no intervention required	1 (1.3)	4 (0.9)	2 (0.4)	3 (2.0)	-
Cardiac perforation (surgical repair)	-	7 (1.5)	1 (0.2)	-	1 (0.4)
Bruising or hematoma	3 (4.0)	4 (0.9)	-	1 (0.7)	2 (0.7)
Major bleed requiring transfusion	-	1 (0.2)	5 (0.9)	-	2 (0.7)
Groin bleeding	-	4 (0.9)	-	1 (0.7)	-
Respiratory failure	-	-	4 (0.7)	-	3 (1.1)
Infection	-	2 (0.4)	-	-	3 (1.1)
Device thrombus	-	2 (0.4)	1 (0.2)	1 (0.7)	-
Arrhythmias	-	2 (0.4)	1 (0.2)	-	-
Transient ischemic attack (TIA)	-	1 (0.2)	2 (0.4)	-	-
AV Fistula	-	1 (0.2)	-	-	1 (0.4)
Chest pain	-	1 (0.2)	1 (0.2)	-	-
Atrial septal defect	-	-	2 (0.4)	-	-
Ventricular tachycardia	-	-	2 (0.4)	-	-
Device migration	-	1 (0.2)	-	-	-
Air embolism	1 (1.3)	-	-	-	-
Inability to move or retrieve device	1 (1.3)	-	-	-	-
Systemic embolism	-	-	-	-	1 (0.4)

Potential adverse events (in alphabetical order) which may be associated with the use of a left atrial appendage closure device include but are not limited to:

- Air embolism
- Airway trauma
- Allergic reaction to contrast media/medications or device materials
- Altered mental status
- Anemia requiring transfusion
- Anesthesia risks
- Angina
- Anoxic encephalopathy
- Arrhythmias
- Atrial septal defect
- AV fistula
- Bruising or hematoma
- Cardiac perforation
- Chest pain/discomfort
- Confusion post procedure
- Congestive heart failure
- Contrast related nephropathy
- Cranial bleed
- Decreased hemoglobin
- Deep vein thrombosis
- Death
- Device embolism
- Device fracture
- Device thrombosis
- Edema
- Excessive bleeding
- Fever
- Groin pain
- Groin puncture bleed
- Hematuria
- Hemoptysis

- Hypotension
- Hypoxia
- Improper wound healing
- Inability to move or retrieve device
- Inability to recapture the device
- Infection/Pneumonia
- Interatrial septum thrombus
- Intratracheal bleeding
- Major bleeding requiring transfusion
- Misplacement of the device / improper seal of the appendage / movement of device from appendage wall
- Nausea
- Oral bleeding
- Pericardial effusion / tamponade
- PFO closure
- Pleural effusion
- Prolonged bleeding from a laceration
- Pseudoaneurysm
- Pulmonary Edema
- Renal failure
- Respiratory insufficiency / failure
- Thrombosis
- Stroke – Ischemic
- Stroke - Hemorrhagic
- Systemic embolism
- TEE complications (throat pain, bleeding, esophageal trauma)
- Thrombocytopenia
- Thrombosis
- Transient ischemic attack (TIA)
- Valvular damage
- Vasovagal reactions

There may be other potential adverse events that are unforeseen at this time.

CLINICAL STUDIES

PILOT Study

Primary Objective: Evaluate the safety of the WATCHMAN® device in subjects with non-valvular atrial fibrillation who required treatment for potential thrombus formation and were eligible for warfarin therapy.

Design: The study was a one-armed observational study intended to document Major Adverse Events (MAEs) specific to the study, which included ischemic stroke, systemic embolism, major bleeding and death as well as complications associated with the WATCHMAN device, both during the procedure and follow-up. Main entry criteria included, but were not limited to, age 18 or older, chronic or paroxysmal AF requiring treatment for potential thrombus formation and eligible for warfarin therapy. Pre-implant, subjects were evaluated with transesophageal echo (TEE) to rule out thrombus. After undergoing the implant procedure, patients were followed at 45 days, 6 months, 12 months, and annually thereafter. Repeat TEE were performed at 45 days and 6 months to verify device position and assess LAA closure.

Demographics: The average CHADS$_2$ in this population was 1.8±1.1. The average age was 69±8 years and the population was 34% female and 100% Caucasian.

Main Results: The WATCHMAN device was successfully implanted in 66/75 (88%) subjects, with discontinuation of warfarin in 68% at 45 days, 92% by six months, and 96% by 60 months. Mean follow-up in this study was 6.1 years. There were no deaths, no device embolizations related to the Gen 2.0/2.5 device, and no evidence of long-term erosion. These results supported progression to a pivotal study.

PROTECT AF Study

Primary Objective: Demonstrate that the WATCHMAN LAAC Therapy is safe and effective in subjects with non-valvular atrial fibrillation who are eligible for warfarin therapy to prevent potential thrombus formation.

Design: The PROTECT AF study was a multi-center prospective randomized design comparing the WATCHMAN Device to a Control group of long-term warfarin therapy. A 2:1 randomization allocation ratio (two Device to one Control) was used with stratification by center.

Main entry criteria included, but were not limited to, at least 18 years of age, non-valvular atrial fibrillation, a CHADS$_2$ score of 1 or greater, and eligibility for long-term warfarin therapy. Following randomization, subjects were assessed at 45 days, 6, 9, 12 months and semi-annually thereafter through 5 years. A non-randomized roll-in phase was added to permit physicians to become experienced with the device implant procedure. Subjects randomized to receive the WATCHMAN device underwent TEE at 45 days, 6 and 12 months to assess device performance. Subjects randomized to the control group remained on warfarin with INR monitored every other week through 6 months and monthly thereafter.

It was hypothesized that subjects randomized to the Device group would have a non-inferior efficacy outcome when compared to the Control group with a posterior probability that the event rate for the Device group was less than 2 times the event rate for the Control group of at least 0.975. Satisfying the criterion for non-inferiority would then meet the criteria for testing for superiority.

The primary efficacy endpoint was the successful treatment of the randomized subject without stroke (including ischemic and hemorrhagic), cardiovascular death (cardiovascular and unexplained) and systemic embolism. The primary safety endpoint was treatment of the subject without the occurrence of life-threatening events as determined by the Clinical Events Committee, which included events such as device embolization requiring retrieval, bleeding events such as pericardial effusion requiring drainage, cranial bleeding events due to any source, gastrointestinal bleeds requiring transfusion and any bleeding related to the device or procedure that necessitates an operation.

Demographics: For subjects randomized to the Device group, the mean CHADS$_2$ score was 2.2±1.2 for the Device group. The mean age was 72 years, 70% were male, and 92% were Caucasian while those subjects in the Control group were characterized with a mean CHADS$_2$ score of 2.3±1.2, a mean age of 73 years, 70% male, and 92% Caucasian. These two populations were well-balanced with no statistically significant differences in baseline demographics.

Main Results: A total of 800 subjects were enrolled, with 707 of them being randomized and the remaining 93 participating in the roll-in group. Of the 707 subjects in the randomized group, 463 were assigned to the WATCHMAN group and 244 assigned to the warfarin control group.

Efficacy: Results for the primary efficacy endpoints of stroke, death (cardiovascular or unexplained) and systemic embolism are displayed in **Table 3**. The primary efficacy event rate was 2.3 events per 100 patient years for the Device group and 3.8 events per 100 patient years for the Control group resulting in a relative risk or rate ratio of 0.60, a 40% lower rate of efficacy events in the Device group than in the Control group. The criterion for non-inferiority and superiority of the Device was met.

Table 3. PROTECT AF Primary Efficacy Results (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

Device Rate (95% CrI)	Control Rate (95% CrI)	Relative Risk (95% CrI)	Posterior Probabilities	
			Non-inferiority	Superiority
2.3 (1.7, 3.2)	3.8 (2.5, 4.9)	0.60 (0.41, 1.05)	>0.999	0.960

CrI = credible interval
Rate = event rate per 100 patient years (calculated as 100*N events/Total patient-years)
Rel. risk = relative risk or rate ratio, calculated as Device rate over Control rate.

Safety: The primary safety rate was 3.6 events per 100 patient years for the Device group and 3.1 events per 100 patient years for the Control group resulting in a relative risk ratio of 1.17. These results are summarized in **Table 4**.

Table 4. Primary Safety Results (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

Device Rate (95% CrI)	Control Rate (95% CrI)	Relative Risk (95% CrI)	Posterior Probabilities	
			Non-inferiority	Superiority
3.6 (2.8, 4.6)	3.1 (2.0, 4.3)	1.17 (0.78, 1.96)	>0.980	0.196

CrI = credible interval
Rate = event rate per 100 patient years (calculated as 100*N events/Total patient-years)
Rel. risk = relative risk or rate ratio, calculated as Device rate over Control rate.

The criterion for non-inferiority of the device to control was met. In addition to these results, 93% of subjects discontinued warfarin therapy by 12 months. There were 74 serious adverse events attributed to the device or implant procedures in 72 subjects (0.16 events/subject). These results demonstrate that while there were risks associated with the device implantation procedure, there were no procedure related deaths, and there was a lower rate of late complications and less severe early complications compared to the control group. Although there is a risk of procedural complications with the WATCHMAN® device, these results demonstrate an overall favorable risk/benefit profile for the Device patients.

CAP Registry

Primary Objective: Demonstrate that the WATCHMAN LAAC Therapy is safe and effective in subjects with non-valvular atrial fibrillation who are eligible for warfarin therapy to prevent potential thrombus formation.

Design: The CAP Registry was a multi-center prospective non-randomized design allowing continued access to the WATCHMAN device during the preparation and evaluation of the PMA for the WATCHMAN device. Up to 30 investigative centers with prior WATCHMAN experience in the PROTECT AF study were allowed to participate and enroll a maximum of 750 subjects. Study participants were required to be at least 18 years of age with non-valvular atrial fibrillation who are eligible for long-term warfarin therapy. Following baseline evaluation and device implant, subjects were seen at 45 days, 6, 9, and 12 months and semi-annually thereafter through 5 years.

The CAP registry evaluated endpoints identical to those used in the PROTECT AF study although there was no pre-defined hypothesis. The primary effectiveness endpoint was the successful treatment of subjects without stroke (including ischemic and hemorrhagic), cardiovascular death (cardiovascular and unexplained) and systemic embolism. The primary safety endpoint was treatment of the subject without the occurrence of life-threatening events as determined by the Clinical Events Committee (CEC), which would include events such as device embolization requiring retrieval, bleeding events such as pericardial effusion requiring drainage, cranial bleeding events due to any source, gastrointestinal bleeding requiring transfusion and any bleeding related to the device or procedure that necessitated a surgical procedure.

Demographics: A total of 26 centers (24 U.S., 2 European) actively participated by enrolling at least one subject in the study. A total of 566 subjects were enrolled. The average CHADS$_2$ score was 2.5±1.2, the mean age was 74 years, and 66% of subjects were male.

Main Results: The WATCHMAN device was successfully implanted in 534/566 (94%) subjects. For the primary efficacy endpoint, a rate of 2.0 events/100 patient-years was observed, with ischemic stroke being the most common event over a mean follow-up duration of 29 months. There were 53 serious procedure or device related adverse events seen in 51 subjects (0.09 events/subject) with decreases in rates of pericardial effusion with tamponade, cardiac perforation, procedural strokes, and device embolization when compared to the PROTECT AF study. There were no procedure-related strokes or deaths during implant of the device with no long-term device migrations or erosions. In addition, 96% of subjects were able to discontinue warfarin therapy by 12 months. The results of this study helped confirm the findings observed in PROTECT AF.

PREVAIL Study

Primary Objective: Evaluate the safety and efficacy of the WATCHMAN LAAC Therapy in subjects with atrial fibrillation who are eligible for long term warfarin therapy.

Design: The PREVAIL study was a multicenter, prospective, randomized (2:1) study comparing the WATCHMAN LAA closure system to warfarin therapy. Subjects were eligible to participate in PREVAIL if they were at least 18 years of age with non-valvular atrial fibrillation and are eligible for long-term warfarin therapy with a CHADS$_2$ score of at least 2. High risk subjects with a CHADS$_2$ score of 1 were also permitted. Similar to the PROTECT AF study, a roll-in phase permitted physicians to gain experience with the device prior to randomization. Following randomization and device implant for those randomized to the Device, subjects were followed at 45 days, 6, 9, and 12 months, semiannually through three years and thereafter annually through five years. All subjects had a baseline INR obtained with monitoring at least every 28 days while on warfarin.

This study had three primary endpoints:

- Comparison of the 18 month rates of the composite endpoint of hemorrhagic stroke, ischemic stroke, systemic embolism or cardiovascular/unexplained death.

  NOTE: This is the same composite endpoint used in the PROTECT AF study.

- Comparison of the 18 month rates of ischemic stroke or systemic embolism excluding the first 7 days post randomization.

- Percentage of subjects that experienced one of the following events between the time of randomization and within 7 days of the procedure or by hospital discharge, whichever is later: all-cause death, ischemic stroke, systemic embolism, or device or procedure related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair. Percutaneous catheter drainage of pericardial effusions, snaring of an embolized device, thrombin injection to treat femoral pseudoaneurysm, and non-surgical treatments of access site complications were excluded from this endpoint.

Demographics: Among subjects randomized to the Device group, the CHADS$_2$ score was 2.6±1.0 with an average age of 74 years. Male subjects represented 68% of the population and 94% were Caucasian. For the Control group, the CHADS2 score was 2.6±1.0. The mean age was 75 years, 75% were male, and 95% were Caucasian. The demographic characteristics in this group were well-balanced with no statistically significant differences.

Main Results: The study enrolled 461 subjects, including 54 roll-in subjects. Of 407 subjects randomized, 269 were assigned to the Device group and 138 were assigned to the Control group to receive warfarin. Mean follow-up was 12 months. Implant success was achieved in 252/265 (95%) subjects who underwent the implant procedure. Credible intervals for the primary endpoints were calculated from a Bayesian model utilizing data from PROTECT AF and CAP Registry as prior information and calculation of time to first event.

First Primary Endpoint: Results for the first primary endpoint of stroke, death (cardiovascular or unexplained) and systemic embolism are displayed in **Table 5**.

Table 5. First Primary Endpoint Results (Intent-to-Treat)

Device 18-Month Rate	Control 18-Month Rate	18-Month Rate Ratio (95% CrI)	Rate Ratio Non-Inferiority Criterion
0.064	0.063	1.07 (0.57, 1.89)	95% CrI Upper Bound < 1.75

CrI = credible interval

There were similar 18-month event rates in the Device and Control groups. The 18-month rate was 0.064 for the Device group and 0.063 for the Control group. These rates yielded a mean 18-month rate ratio of 1.07 with a 95% credible interval of 0.57 to 1.89. The upper bound of 1.89 was not lower than the non-inferiority margin of 1.75 defined in the statistical analysis plan, therefore statistical non-inferiority was not achieved.

Second Primary Endpoint: Results for the second primary endpoint are displayed in **Table 6**. The 18-month rate is the probability of an event occurring within 18 months. The 18-month rate ratio is a mean of the rate ratios.

Table 6. Second Primary Endpoint Results (Intent-to-Treat)

Device 18-Month Rate	Control 18-Month Rate	18-Month Rate Ratio (95% CrI)	Rate Ratio Non-Inferiority Criterion	18-Month Rate Difference (95% CrI)	Rate Difference Non-Inferiority Criterion
0.0253	0.063	1.07 (0.57, 1.89)	95% CrI Upper Bound < 1.75	0.0053 (-0.0190, 0.0273)	95% CrI Upper Bound < 0.0275

CrI = credible interval

The 18-month rate was 0.0253 for the Device group and 0.0200 for the Control group. The non-inferiority criterion pre-defined in the statistical analysis plan allowed for one of the two following scenarios to statistically achieve non-inferiority of the second primary endpoint:

1. The 18-month rate ratio had to have a 95% upper credible interval less than 2.0. The observed upper bound was 4.2 exceeding the allowable limit. Or

2. The 18 month rate difference must have a 95% upper credible interval less than 0.0275. The 18-month rate difference was 0.0053 with an upper bound of 0.0273, therefore achieving the non-inferiority criterion.

Non-inferiority of the Device group to the Control group was achieved for the second primary endpoint of ischemic stroke or systemic embolism greater than 7 days post randomization.

Third Primary Endpoint: Results for the third primary endpoint are displayed in **Table 7**.

Table 7. Third Primary Endpoint Results (Intent-to-Treat)

Device Group		
N Subjects	% (n/N)	95% Crl
269	2.2% (6/269)	2.652%

Crl is one-sided, N = number, Crl = credible interval

Success for this endpoint was achieved if the percentage of subjects experiencing one of the events was statistically less than the performance goal, defined as 2.67%, with an upper bound of the one-sided 95% credible interval less than the performance goal. There were six (6) events meeting the third primary endpoint definition in 269 subjects. Therefore, 2.2% of subjects experienced an event and a one-sided 95% credible interval upper bound was 2.652%. Success of the third primary endpoint was achieved.

In addition to these results, 99% of subjects in the Device group followed for at least 12 months had discontinued warfarin. There were 28 serious adverse events attributed to the device and/or procedure (0.11 events/subject).

The PREVAIL study confirmed the findings from the earlier PROTECT AF study by demonstrating similar or better efficacy results than warfarin therapy. PREVAIL also demonstrated that high implant success rates and high rates of warfarin discontinuation may be achieved while reducing the number of procedural complications.

ASAP Study

Primary Objective: Characterize the performance of the WATCHMAN® device in non-valvular atrial fibrillation (AF) subjects with contraindications to warfarin therapy. Subjects were prescribed aspirin and clopidogrel therapy post implant for 6 months rather than the usual six weeks of warfarin therapy.

Design: The study was a multicenter, prospective, non-randomized feasibility study of the WATCHMAN device in warfarin contraindicated subjects conducted at four investigational centers in Europe. In addition to a contraindication for warfarin, study participants were required to be at least 18 years of age and have recurrent non-valvular atrial fibrillation with a CHADS$_2$ score of 1 or greater, and an LVEF at least 30% or greater. Subjects were followed at 3, 6, 12, 18, and 24 months with TEE examinations at 3 and 12 months to assess the WATCHMAN device. This study did not have formal hypothesis testing but instead used descriptive statistics to characterize event rates for all-cause mortality, ischemic and hemorrhagic stroke, and device thrombus as well as serious procedure or device-related adverse events. This study also employed covariate analyses to explore whether baseline clinical measures were associated with these study outcomes.

Demographics: The average CHADS$_2$ in this population was 2.8±1.2. The average age was 73±7 years and the population was 36% female. The most common contraindication to warfarin therapy was a history of bleeding tendencies (67%).

Main Results: The WATCHMAN device was successfully implanted in 142/150 (95%) subjects with a mean follow-up duration of 17 months. There were no deaths and no evidence of long-term erosion. Event rates observed in the study were:

Event	Events/Pt-yrs (Rate per 100 Pt-yrs)
Death (All-Cause)	11/213.7 (5.1)
Stroke	5/209.0 (2.4)
- Ischemic Stroke	4/210.4 (1.9)
- Hemorrhagic Stroke	1/212.3 (0.5)
Device Thrombus	8/205.4 (3.9)

A total of 15 serious procedure or device-related adverse events (0.10 events/subject) were observed in this population, which is comparable to that seen in patients eligible for warfarin therapy who received the WATCHMAN device. Covariate analysis showed that an increased risk of stroke was associated with greater age and higher CHADS$_2$ score. All stroke and ischemic stroke rates in ASAP were similar to those observed in the randomized non-inferiority PROTECT AF study despite having a higher CHADS$_2$ stroke risk. These results suggest that it may be safe to implant the WATCHMAN device in patients with contraindications to warfarin therapy.

HOW SUPPLIED
- The WATCHMAN LAA Closure Device is pre-loaded in the Delivery System.
- The WATCHMAN Access System is packaged separately.

- The WATCHMAN LAA Closure products are supplied STERILE using an ethylene oxide (EO) process.
- Do not use if package is opened or damaged.
- Do not use if labeling is incomplete or illegible.

Note: Contents of inner package are STERILE.

Handling and Storage
Store in a cool, dry, dark place.

OPERATIONAL INSTRUCTIONS
Pre-Procedural Instructions
A baseline TEE should be performed to verify that a WATCHMAN LAA Closure Device may be implanted.

1. Assess the following through multiple imaging planes (0° - 135° sweep):
   - LAA size /shape, number of lobes in LAA, and location of lobes to ostium.
   - Confirm the absence of thrombus (use Color Doppler and echo contrast as necessary).
2. Record LAA ostium and LAA length measurements (0° - 135° sweep). Measure the LAA ostium at approximately these angles.
   - at 0° measure from coronary artery marker to a point 2 cm from tip of the "limbus"
   - at 45° measure from top of the mitral valve annulus to a point 2 cm from tip of the "limbus"
   - at 90° measure from top of the mitral valve annulus to a point 2 cm from tip of the "limbus"
   - at 135° measure from top of the mitral valve annulus to a point 2 cm from tip of the "limbus"

Measured maximum LAA ostium width must be ≥17 mm or ≤31 mm to accommodate available device sizes.

Note: The maximum LAA ostium and LAA length measurements determine device size selection.

PROCEDURAL INSTRUCTIONS
Equipment Needed for Implantation Procedure
- WATCHMAN Delivery System(Delivery Catheter and LAA Closure Device)
- Venous Introducer (optional)
- Standard transseptal access system
- 0.035 in guidewire (exchange length extra support)
- 6F Pigtail Catheter
- WATCHMAN Access System (Access Sheath/Dilator)

Implantation Procedure

NOTE: The use of echocardiographic imaging is required (TEE is recommended as an aid in placing the WATCHMAN Device).

NOTE: Patients should be fully heparinized throughout the procedure with a recommended minimum activated clotting time (ACT) of 200-300 seconds after transseptal puncture.

1. Use standard practice to puncture vessel and insert 0.035 in guidewire and vessel dilator. Use a standard transseptal access system to cross inter-atrial septum.
2. Exchange crossing sheath with exchange length extra support 0.035 in guidewire. Position guidewire in left upper pulmonary vein (LUPV) or loop in left atrium.
3. Prepare WATCHMAN Access System.
   A. Remove Access Sheath and Dilator under sterile conditions.
   B. Inspect prior to use to ensure no damage. Inspect sterile package and WATCHMAN Access System prior to use. If sterile barrier has been compromised in any way, DO NOT USE.
   C. Flush Access Sheath and Dilator with sterile saline prior to use.
   D. Insert Dilator into hemostasis valve of Access Sheath.
4. Advance WATCHMAN Access System over guidewire into left atrium (LA). As Access Sheath nears center of LA, hold Dilator and advance Access Sheath into initial position in LA or ostium of LUPV.

PRECAUTION: Use caution when introducing WATCHMAN Access System to prevent damage to cardiac structures.

5. Remove Dilator and guidewire, leaving Access Sheath. Allow back bleed to minimize potential for introducing air before tightening valve. Flush with saline.
6. Confirm LAA size and select appropriate WATCHMAN LAA Closure Device.
   A. Using TEE, measure LAA ostium width and LAA length in 3-4 views (0°, 45°, 90°, 135°).
   B. Record multiple angles on cine with contrast prior to advancing Access Sheath into LAA. Use fluoro guidance while advancing pigtail catheter, or Access Sheath. Stop if resistance is felt.
   C. Choose a device based on **maximum** LAA ostium width recorded. Use **Table 8** as a guide.

   NOTE: LAA anatomy should accommodate a Device as described in **Table 8**.

Table 8. WATCHMAN LAA Closure Device Selection

Max LAA Ostium (mm)	Device Diameter (mm)
17 – 19	21
20 – 22	24
23 – 25	27
26 – 28	30
29 – 31	33

   D. Carefully advance pigtail catheter through Access Sheath into distal LAA under fluoro guidance. Carefully advance Access Sheath over pigtail catheter until Access Sheath marker band corresponding to Device size (see Figure 1) is at or just distal to LAA ostium. Slowly remove pigtail catheter.
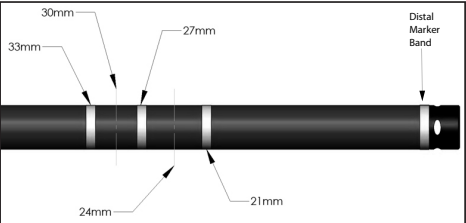
Figure 1. WATCHMAN Access Sheath Marker Bands

7. Prepare WATCHMAN Delivery System
   A. Remove Delivery System under sterile conditions.
   B. Inspect prior to use to ensure no damage to handle, catheter connections and Device (through Delivery System).

   NOTE: If sterile barrier has been compromised in any way, or Delivery System appears damaged DO NOT USE.

   C. Confirm that the distal tip of the Device is aligned with marker band on Delivery System.

   PRECAUTION: Do not allow WATCHMAN Device to protrude to prevent damage to Delivery Catheter.

   D. Flush system with saline removing all air and maintaining fluid throughout Delivery System. Open and flush proximal valve.

   NOTE: To avoid introducing air, apply pressurized saline bag to sideport of Access Sheath, or submerge Access Sheath hub in saline. Saline may be dripped from Delivery System during introduction into Access Sheath by injecting through flush port.

8. Loosen proximal valve of Access Sheath allowing bleed back before inserting Delivery System. Note: Hemostasis valve should spin freely (fully open).
9. To avoid introduction of air, slowly advance Delivery System into Access Sheath under fluoro guidance.

   PRECAUTION: Use caution when introducing Delivery System to prevent damage to cardiac structures.

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10. On fluoro, align most distal marker band on Delivery System with most distal marker band on Access Sheath. Once bands are aligned, stabilize Delivery System, retract Access Sheath and snap together as Access Sheath/Delivery System Assembly.

11. Using fluoro and TEE confirm position of Delivery System tip before deploying the Device.

NOTE: To inject contrast, flush catheter or measure power injector pressure while inserting Delivery System into Access Sheath. Contrast syringe or manifold must be attached to flush port of Delivery System.

PRECAUTION: If using a power injector, the maximum pressure **should not** exceed 100 psi.

12. If repositioning is required, unsnap and slowly remove Delivery System from Access Sheath. If necessary reinsert pigtail catheter to reposition Access Sheath. Reinsert Delivery System as described in Steps 9 and 10.

13. Deploy WATCHMAN® Device by loosening valve on Delivery System and holding deployment knob stationary while retracting Assembly to completely deploy Device. Leave core wire attached.

14. Device release criteria:

A. **Position:** Plane of maximum diameter is at or just distal to and spans entire LAA Ostium (See Figure 2).

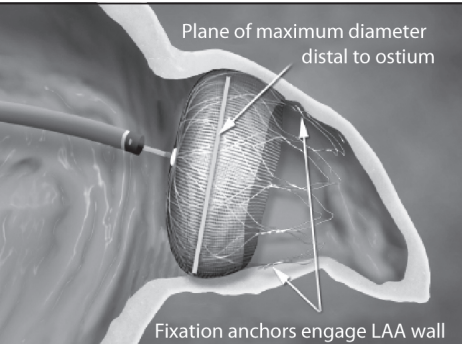Plane of maximum diameter distal to ostium

Fixation anchors engage LAA wall

Figure 2. WATCHMAN LAA Closure Device Position and Size

B. **Anchor:** Gently pull back then release deployment knob to visualize movement of Device and LAA together.

C. **Size (compression):** Measure plane of maximum diameter of Device (See Figure 5). Use **Table 9** as a guide.

D. **Seal:** Ensure all lobes are distal to Device and sealed.

Table 9. WATCHMAN LAA Closure Device Diameter

Original Diameter (mm)	Deployed Diameter (80-92% of original) (mm)
21	16.8-19.3
24	19.2-22.1
27	21.6-24.8
30	24.0-27.6
33	26.4 -30.4

15. Partial Device Recapture

NOTE: Partially recapture and redeploy WATCHMAN Device if too distal to LAA ostium

A. Advance tip of Access/Delivery System Assembly up to Device (do not unsnap). Fix deployment knob position with right hand and gently advance Access/Delivery System Assembly over shoulders of Device. Position right thumb against Delivery System hub for stability. Resistance will be felt as Device shoulders collapse. Continue to advance Assembly up to but not past fixation anchors. When resistance is felt a second time (anchor contact), stop, tighten hemostasis valve.

NOTE: If Device is retrieved past fixation anchors, recapture fully and replace Delivery System. Refer to Step 16. The WATCHMAN Device and Delivery System are for single use only. Do not reuse or resterilize.

B. Reposition Access Delivery/System Assembly proximally and re-deploy by holding deployment knob and retracting Access Sheath until Device is completely deployed. Leave core wire attached.

WARNING: Do not release the WATCHMAN Device from the core wire if the Device does not meet release criteria (Step 14).

16. Full Device recapture.

NOTE: Fully recapture the Device if too proximal or does not meet release criteria

A. Advance tip of Access/Delivery System Assembly up to face of Device (do not unsnap).

B. Fix deployment knob with right hand and gently advance Access/Delivery System Assembly over shoulders of Device. Position right thumb against Delivery System for stability. Resistance will be felt as Device shoulders collapse. Continue to advance Assembly until Device is completely collapsed and recaptured (past anchors).

C. Withdraw Device until distal tines are proximal to marker band then tighten hemostasis valve.

D. Unsnap Delivery System from Access Sheath while maintaining position. Slowly remove Delivery System.

E. Insert pigtail catheter to reposition Access Sheath in LAA if necessary.

F. Repeat Steps 7-14 with new Delivery System.

17. WATCHMAN Device Release: Confirm proper position, anchor, size, and seal, and then advance Assembly to face of Device. Rotate deployment knob counter clockwise 3-5 full turns. Confirm core wire is disconnected.

18. Remove Access Sheath and Delivery System based on parameters for hemostasis.

19. Use standard of care for post procedure bleeding at access site.

20. Post Procedure Information

A. Post-procedure warfarin therapy is required in ALL patients receiving a Device who are eligible for warfarin therapy or other equivalent oral anticoagulant per institution's protocol. Patients should remain on 81-100 mg of aspirin and warfarin for a minimum of 45 days post implant (INR 2.0-3.0). At 45 days post implant perform Device assessment with TEE. Cessation of warfarin is at physician discretion. Patients ceasing warfarin should begin clopidogrel 75mg daily and increase aspirin dosage to 300-325 mg daily for 6 months post-implant and remain on aspirin 300- 325 mg indefinitely.

B. At 45 days assess WATCHMAN Device with TEE.
- Confirm absence of intra-cardiac thrombus.
- Perform color Doppler assessment to include the device/LAA border at the following approximate TEE angles (0°, 45°, 90°and 135°). Measure any residual jet around the device if necessary.

C. Prescribe appropriate endocarditis prophylaxis for 6 months following Device implantation. The decision to continue endocarditis prophylaxis beyond 6 months is at physician discretion.

WARRANTY

Boston Scientific Corporation (BSC) warrants that reasonable care has been used in the design and manufacture of this instrument. **This warranty is in lieu of and excludes all other warranties not expressly set forth herein, whether express or implied by operation of law or otherwise, including, but not limited to, any implied warranties of merchantability or fitness for a particular purpose.** Handling, storage, cleaning and sterilization of this instrument as well as other factors relating to the patient, diagnosis, treatment, surgical procedures and other matters beyond BSC's control directly affect the instrument and the results obtained from its use. BSC's obligation under this warranty is limited to the repair or replacement of this instrument and BSC shall not be liable for any incidental or consequential loss, damage or expense directly or indirectly arising from the use of this instrument. BSC neither assumes, nor authorizes any other person to assume for it, any other or additional liability or responsibility in connection with this instrument. **BSC assumes no liability with respect to instruments reused, reprocessed or resterilized and makes no warranties, express or implied, including but not limited to merchantability or fitness for a particular purpose, with respect to such instruments.**

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Appendix C: Entrance Criteria

PROTECT AF Study Inclusion Criteria

A patient was enrolled in the study if all of the following inclusion criteria were met:

– The patient is 18 years of age or older

– The patient has documented paroxysmal, persistent, or permanent non-valvular atrial fibrillation (i.e., the patient has not been diagnosed with rheumatic mitral valvular heart disease)

– The patient is eligible for long-term warfarin therapy

– The patient is eligible to come off warfarin therapy if the LAA is sealed (i.e., the patient has no other conditions that would require long-term warfarin therapy suggested by current standard medical practice)

– The patient has a calculated CHADS$_2$ score of 1 or greater

– The patient or legal representative is able to understand and willing to provide written informed consent to participate in the trial

– The patient is able and willing to return for required follow-up visits and examinations

PROTECT AF Exclusion Criteria

A patient was excluded from the study if any of the following clinical exclusion criteria were met:

– The patient suffers from New York Heart Association Class IV Congestive Heart Failure

– The patient has had a recent MI (within 3 months)

– The patient has an atrial septal defect (ASD) and/or atrial septal repair or closure device

– The patient had a single occurrence of AF

– The patient has an ablation procedure planned within 30 days of potential WATCHMAN Device implant

– The patient has a planned cardioversion 30 days post implant of the WATCHMAN Device

– The patient has a resting heart rate > 110 bpm

– The patient had a transient case of AF (i.e., secondary to recent coronary artery bypass graft (CABG) (within 3 months), etc.)

– The patient has an implanted mechanical valve prosthesis

– The patient's left atrial appendage is obliterated

- The patient has undergone heart transplantation

- The patient has symptomatic carotid disease (i.e., carotid stenosis ≥ 50% associated with ipsilateral transient or visual transient ischemic attack (TIA) evidenced by amaurosis fugax, ipsilateral hemispheric TIAs or ipsilateral stroke within 6 months)

- The patient had a prior embolic stroke or TIA within the last 30 days

- The patient requires long-term warfarin therapy (refer to protocol for additional details)

- The patient is contraindicated for warfarin therapy

- The patient has thrombocytopenia (< 100,000 platelets/mm3) or anemia with hemoglobin concentration of < 10 g/dl

- The patient is contraindicated for aspirin

- The patient is actively enrolled in another IDE or IND investigation of a cardiovascular device or an investigational drug (post-market study participation is acceptable)

- The patient is pregnant or pregnancy is planned during the course of the investigation if patient is of child bearing potential

- The patient has an active infection of any kind

- The patient has a terminal illness with life expectancy less than two years

- The patient has a life expectancy of less than two years

PROTECT AF Echo Exclusion Criteria

A patient was excluded from the study if any of the following echocardiographic exclusion criteria (as assessed via transthoracic (TTE) and TEE) were met:

- The patient has LVEF < 30%

- The patient has intracardiac thrombus or dense spontaneous echo contrast as visualized by TEE within 2 days prior to implant

- The patient has a high risk patent foramen ovale (PFO) (refer to protocol for additional details):

- The patient has significant mitral valve stenosis (i.e., MV <1.5 cm2)

- The patient has an existing pericardial effusion of > 2 ± 1 mm

- The patient has complex atheroma with mobile plaque of the descending aorta and/or aortic arch

- The patient has a cardiac tumor

PREVAIL Inclusion Criteria

Patients were required to meet all of the following inclusion criteria:

1. The patient is 18 years of age or older
2. The patient has documented paroxysmal, persistent, or permanent non-valvular atrial fibrillation (i.e., the patient has not been diagnosed with rheumatic mitral valvular heart disease)
3. The patient is eligible for long-term warfarin therapy
4. The patient is eligible to come off warfarin therapy if the LAA is sealed (i.e., the patient has no other conditions that would require long-term warfarin therapy suggested by current standard medical practice)
5. The patient has a calculated $CHADS_2$ score of 2 or greater; Patients with a $CHADS_2$ score of 1 may be included if any of the following apply (according to the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation patients requiring warfarin therapy) :
   - The patient is a female age 75 or older
   - The patient has a baseline LVEF $\geq$ 30 and < 35%
   - The patient is age 65-74 <u>and</u> has diabetes or coronary artery disease
   - The patient is age 65 or greater <u>and</u> has documented congestive heart failure
6. The patient or legal representative is able to understand and willing to provide written informed consent to participate in the study
7. The patient is able and willing to return for required follow-up visits and examinations

PREVAIL Clinical Exclusion Criteria

Patients were excluded from the study if they meet any of the following exclusion criteria:

1. The patient requires long-term warfarin therapy (i.e., even if the device is implanted, the patients would not be eligible to discontinue warfarin due to other medical conditions requiring chronic warfarin therapy). Additionally, a patient with any of the following is excluded:
   - Thrombosis occurring at a young age (<40 years old)
   - Idiopathic or recurrent venous thromboembolism
   - Thrombosis at an unusual site (i.e., cerebral veins, hepatic veins, renal veins, inferior vena cava, mesenteric veins)
   - Family history of venous thromboembolism or of inherited prothrombotic disorder
   - Recurrence or extension of thrombosis while adequately anticoagulated
2. The patient is contraindicated for warfarin therapy or cannot tolerate long-term warfarin therapy

3. The patient is contraindicated or allergic to aspirin
4. The patient is indicated for clopidogrel therapy or has taken clopidogrel within 7 days prior to enrollment
5. The patient had or is planning to have any cardiac or non-cardiac interventional or surgical procedure within 30 days prior to or 60 days after the WATCHMAN device implant (e.g., cardioversion, ablation, cataract surgery)
6. The patient had a prior stroke or TIA within the 90 days prior to enrollment
7. The patient has had an MI within 90 days prior to enrollment
8. The patient has a history of atrial septal repair or has an ASD/PFO device
9. The patient has an implanted mechanical valve prosthesis
10. The patient suffers from New York Heart Association Class IV Congestive Heart Failure
11. The patient has symptomatic carotid disease (defined as >50% stenosis with symptoms of ipsilateral transient or visual TIA evidenced by amaurosis fugax, ipsilateral hemispheric TIAs or ipsilateral stroke); if patient has a history of carotid stent or endarterectomy the patient is eligible if there is < 50% stenosis
12. The patient's AF is defined by a single occurrence of AF
13. The patient had a transient case of AF (i.e., secondary to CABG, interventional procedure, etc.)
14. The patient's left atrial appendage is obliterated
15. The patient has undergone heart transplantation
16. The patient has an active infection of any kind
17. The patient has a resting heart rate > 110 bpm
18. The patient has thrombocytopenia (defined as < 70,000 platelets/mm^3) or anemia with hemoglobin concentration of < 10 g/dl (i.e., anemia as determined by the investigator which would require transfusion)
19. The patient is actively enrolled or plans to enroll in a concurrent clinical study in which the investigational drug or device is of cardiovascular/neurologic nature or may confound the results of the study (including studies for treatment of arrhythmias)
20. The patient participated in the PROTECT AF study or the CAP Registry
21. The patient is pregnant or pregnancy is planned during the course of the investigation
22. The patient has a life expectancy of less than two years
23. The patient is unable to complete follow-up visits for the duration of the study

PREVAIL Echocardiographic Exclusion Criteria

Patients were excluded from the study if any of the following echocardiographic exclusion criteria (as assessed via TTE and TEE) were met:

1. The patient has LVEF < 30%
2. The patient has intracardiac thrombus or dense spontaneous echo contrast as visualized by TEE and determined by the echocardiographer within 2 days prior to implant
3. The patient has an existing pericardial effusion > 2mm
4. The patient has a high risk patent foramen ovale (PFO), defined as an atrial septal aneurysm (excursion > 15mm or length $\geq$ 15mm) or large shunt (early, within 3 beats and/or substantial passage of bubbles)
5. The patient has significant mitral valve stenosis (i.e., MV <1.5 cm^2)
6. The patient has complex atheroma with mobile plaque of the descending aorta and/or aortic arch
7. The patient has a cardiac tumor

Appendix D: Adverse Event Handling Procedures

PROTECT Adverse Event Handling Procedures

Investigators must document all adverse events (AEs) which study patients experience during participation in this investigation. Each reported event must be appropriately documented to include the event's seriousness, relatedness and resolution, and the following requirements should be followed:

A *Serious Adverse Event Fax Notification Form* must be completed for all Serious Adverse Events (SAE), deaths or Unanticipated Adverse Device Effects (UADE) that occur during the course of the study. A Serious Adverse Event is defined as: Any untoward medical occurrence that:
- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity.

The *SAE Fax Notification Form* should be faxed to Atritech within 24 hours of when the investigator learns of the event. Source documentation on the event should begin immediately for CEC adjudication.

An *Adverse Event Case Report Form* must be completed for all AEs and events that may be related to the device or procedure.

All reported events that remain unresolved should be re-assessed at each subsequent follow-up interval until the event resolves or the patient's study participation is complete.

All AEs reported on an *Adverse Event Case Report Form* will be adjudicated by the Clinical Events Committee.

PREVAIL Adverse Event Handling Procedures

Adverse events reported by the investigational sites were adjudicated by the CEC. Adverse experiences that required reporting included any adverse event with clinical symptoms that could possibly be contributed to any of the following:

- The WATCHMAN device

- The WATCHMAN implant procedure

- The use of study mandated medications warfarin, clopidogrel or aspirin (i.e., gastrointestinal bleeding due to warfarin or an allergic reaction to clopidogrel)

- Any study required procedures (i.e., clinical complications from protocol required TEE)

The following adverse events were also required to be reported:

- Neurological events including, but not limited to, stroke, TIA or seizure which are not pre-study conditions

- Any events possibly related to the study endpoints of stroke, systemic embolism, death, etc.

- Thrombosis

- Bleeding complications requiring intervention or transfusion of blood

- Any potential UADE

Each adverse event was evaluated by the investigator for relatedness and seriousness.

Appendix E: CEC Adverse Event Definitions

PROTECT AF CEC Adverse Event Definitions

Non-event definition

Originally defined 9-15-05 revised for clarity 5-16-07

The definition of a Non-event is an event that is not study related, or of minor or not lasting clinical significance, or a non-specific symptom.

Ischemic Stroke

Sudden onset of a focal neurological deficit with symptoms and/or signs persisting more than 24 hours or symptoms less than 24 hours with CT or MRI evidence of tissue loss without hemorrhage.

- **Major Stroke**: A New Neurological Deficit, Which Is Present After 7 Days and increases the NIHSS by ≥4.

- **Minor Stroke**: A new neurological deficit, which either resolves completely within 7 days or increases the NIHSS by ≤3.

Hemorrhagic Stroke

Sudden onset of a focal neurological deficit with CT or MRI evidence of tissue loss with evidence of blood vessel hemorrhage.

Hemorrhagic strokes can be divided into EDH, SDH, SAH, IPH/ICH (four localizations). Some of IPH are ischemic infarcts with hemorrhagic conversion; some are drugs, HTN, AVM, and aneurysm.

Subdural Hematoma

A traumatic hemorrhage limited to the subdural compartment is defined as a non-event.

Cardiovascular Death

A cardiovascular death is a death from a cardiovascular event including sudden death, MI, CVA, cardiac arrhythmia and heart failure. In addition, any death caused by an undetermined etiology will be cardiovascular.

Systemic Embolism

Abrupt vascular insufficiency associated with clinical or radiologic evidence of arterial occlusion in the absence of other likely mechanisms (e.g., atherosclerosis, instrumentation). In the presence of atherosclerotic peripheral vascular disease, diagnosis of embolism to the lower extremities requires arteriographic demonstration of abrupt arterial occlusion.

Pericardial Effusion

Pericardial Effusion is defined by the clinical therapy associated with the effusion. The following definitions of pericardial effusion were written and approved by the CEC, then submitted to and approved by the FDA.

Pericardial Effusion (Non-Serious)

Pericardial Effusion (Non-Serious) is defined as increased fluid within the pericardial sac that did not cause circulatory compromise and did not require drainage.

Pericardial Effusion (Serious)

- **Cardiac Tamponade** - any pericardial effusion requiring percutaneous treatment.
- **Cardiac Perforation** - any pericardial effusion requiring surgical intervention.

Epistaxis

A nose bleed was considered a bleeding event if any of the following were fulfilled: a) the patient sought medical attention from a physician or visited the emergency room, b) the bleeding required an intervention, i.e., nasal pack. A nose bleed that was self-reported and had no supporting evidence was categorized as a non-event.

Gastrointestinal Bleeding

A gastrointestinal bleed was considered a bleeding event if any of the following were fulfilled: a)vomit containing frank blood that tested positive for blood; b) frank blood per rectum or melena stools: c) endoscopically-confirmed bleeding. Insignificant hemorrhoid bleeding described as blood on toilet paper was not considered a bleeding event.

Hematuria

Hematuria was considered a bleeding event if there was overt spontaneous bleeding confirmed by objective evidence and patient sought medical attention from a physician or visited an emergency room.

Hematoma (including surgical site)

A hematoma which resolves with manual pressure alone with no transfusion will be considered a non-event.

PREVAIL CEC Adverse Event Definitions

Non-Event

The definition of a non-event is an event that is not study related, or of minor or not lasting clinical significance, or a non-specific symptom.

Ischemic Stroke

Sudden onset of a focal neurological deficit with symptoms and/or signs persisting more than 24 hours or symptoms less than 24 hours with CT or MRI evidence of tissue loss without hemorrhage.

- **Major Stroke**: A new neurological deficit, which is present after 7 days and increases the NIHSS by ≥4.

- **Minor Stroke**: A new neurological deficit, which either resolves completely within 7 days or increases the NIHSS by ≤3.

Hemorrhagic Stroke

Symptomatic intracranial hemorrhage due to any cause.

Intracranial Bleed

Asymptomatic intracranial hemorrhage.

Cardiovascular or Unexplained Death

A cardiovascular death is a death from a cardiovascular event including sudden death, MI, cardiac arrhythmia, and heart failure. In addition, any death caused by an undetermined etiology will be cardiovascular.

Systemic Embolism

Abrupt vascular insufficiency associated with clinical or radiologic evidence of arterial occlusion in the absence of other likely mechanisms (e.g., atherosclerosis, instrumentation). In the presence of atherosclerotic peripheral vascular disease, diagnosis of embolism to the lower extremities requires arteriographic demonstration of abrupt arterial occlusion.

Pericardial Effusion

Pericardial Effusion is defined by the clinical therapy associated with the effusion:

Pericardial Effusion

An observed pericardial effusion not necessitating percutaneous drainage nor surgical repair.

Pericardial Effusion with Tamponade

A pericardial effusion resulting in percutaneous treatment/drainage.

Cardiac Perforation

A pericardial effusion resulting in surgical intervention/repair.

Epistaxis

A spontaneous nose bleed where the patient sought medical attention from a physician, requires blood transfusion, or visited an emergency room.

Gastrointestinal Bleeding

A gastrointestinal bleed is considered a bleeding event if any of the following are documented in medical records: a) vomit containing frank blood that tested positive for blood; b) frank blood per rectum or melena stools; c) endoscopically-confirmed bleeding. Insignificant hemorrhoid bleeding described as blood on toilet paper or self-reported episodes without medical documentation is not considered a bleeding event.

Hematuria

Hematuria is considered a bleeding event if there is overt spontaneous bleeding confirmed by objective evidence and patient sought medical attention from a physician, requires blood transfusion, or visited an emergency room.
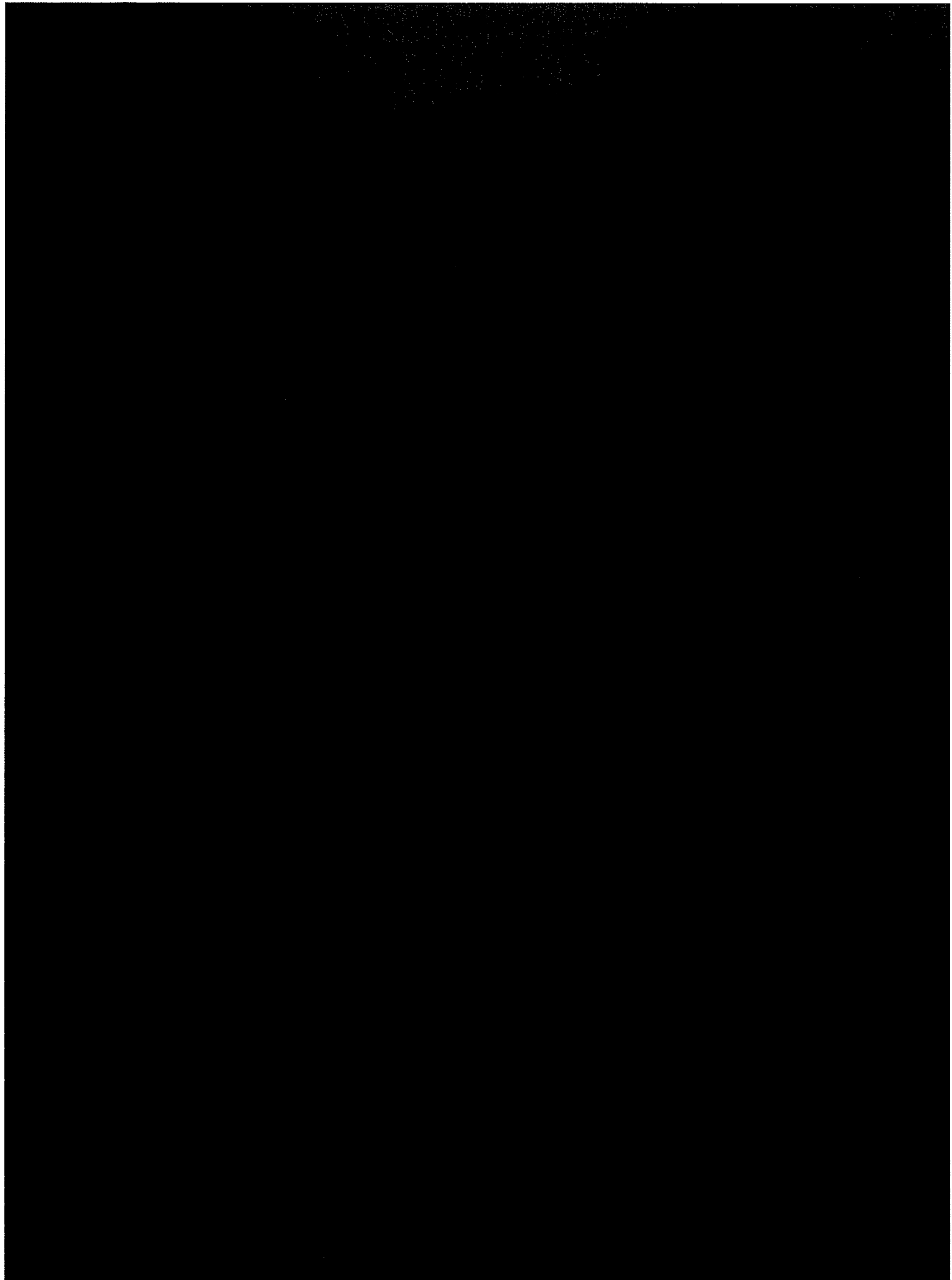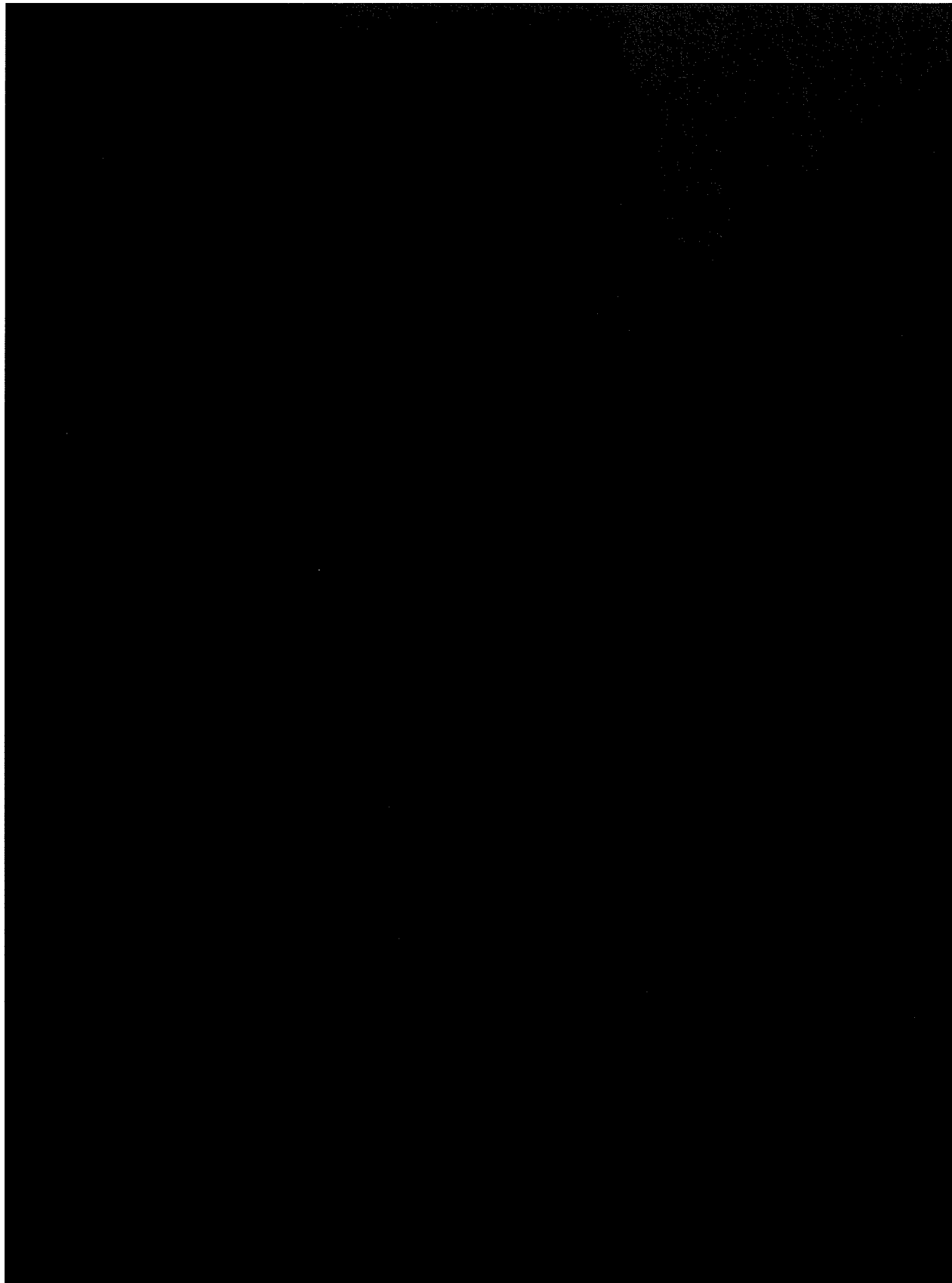
Hematoma (including surgical site)

A hematoma which resolves with manual pressure alone with no transfusion is considered a non-event.
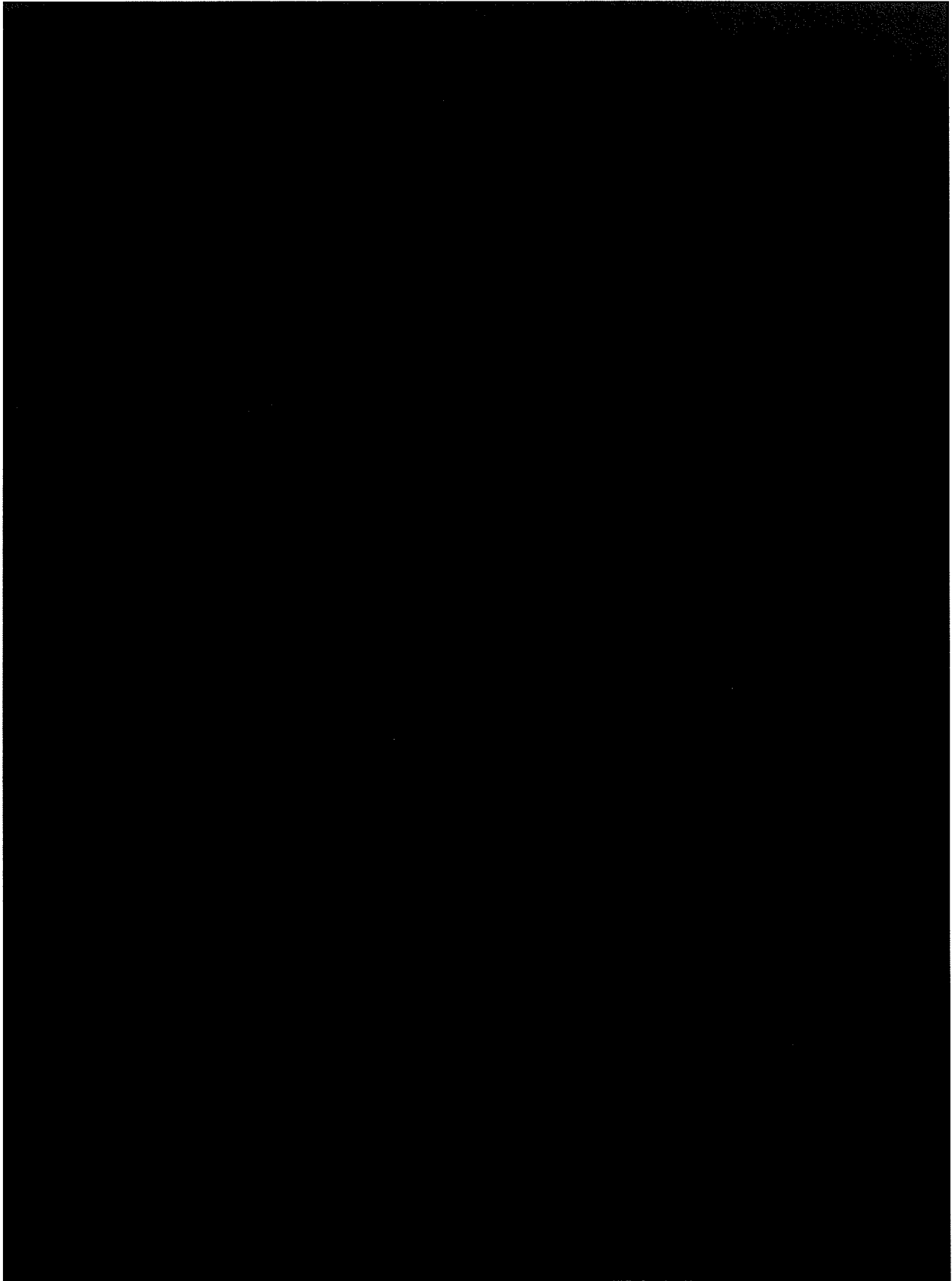
Appendix F: Single Center Violation of Good Clinical Practice and Sensitivity Analysis
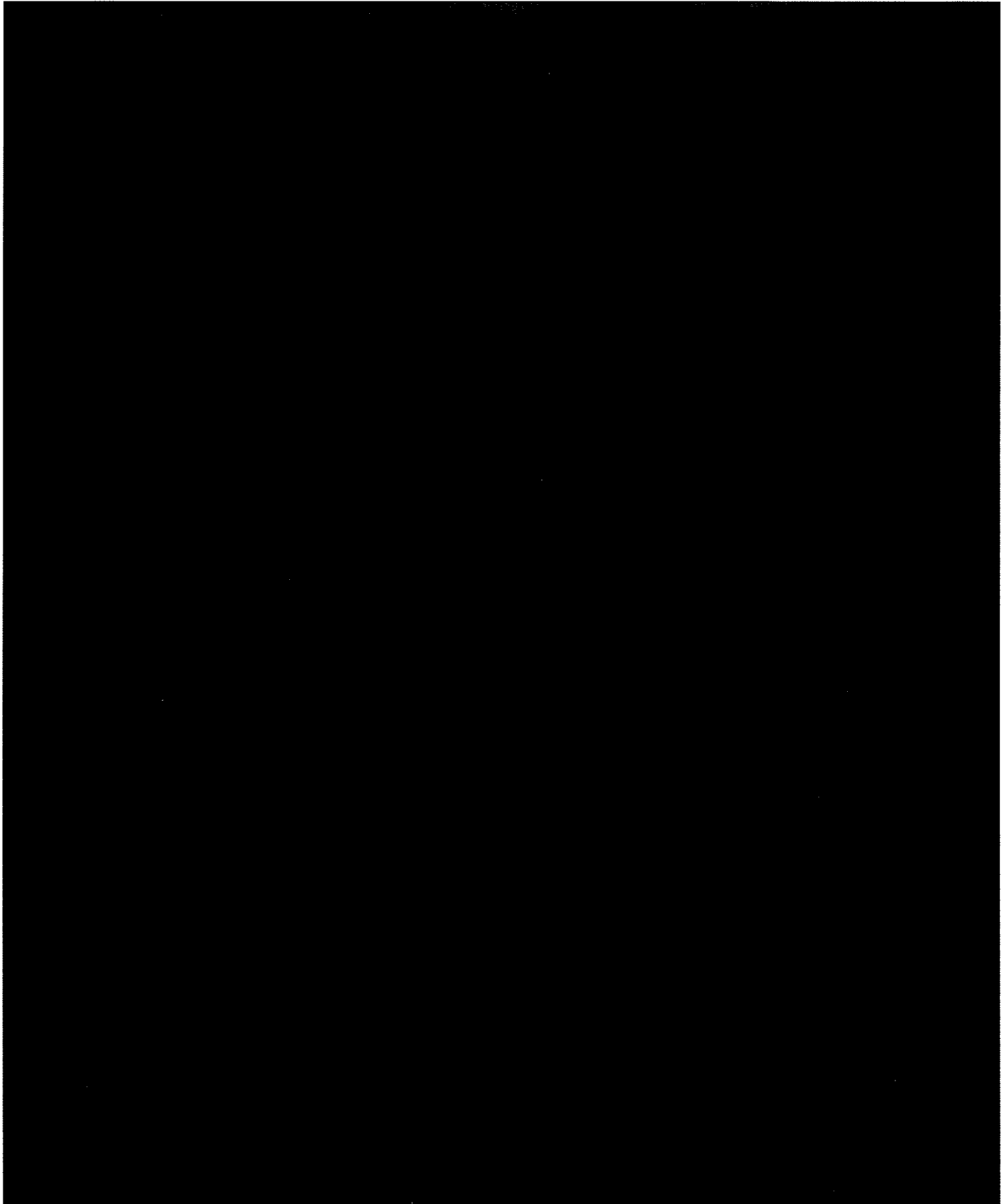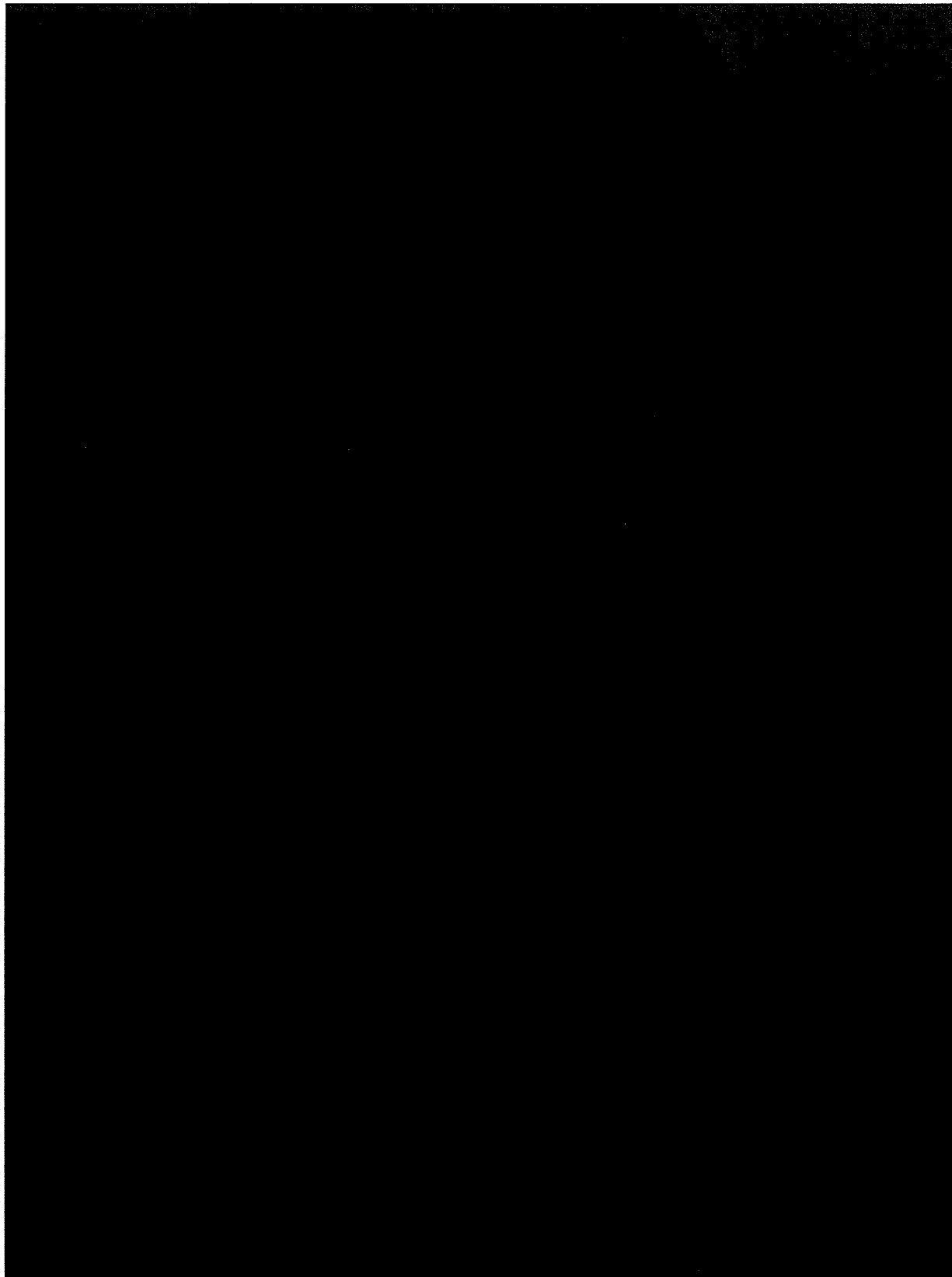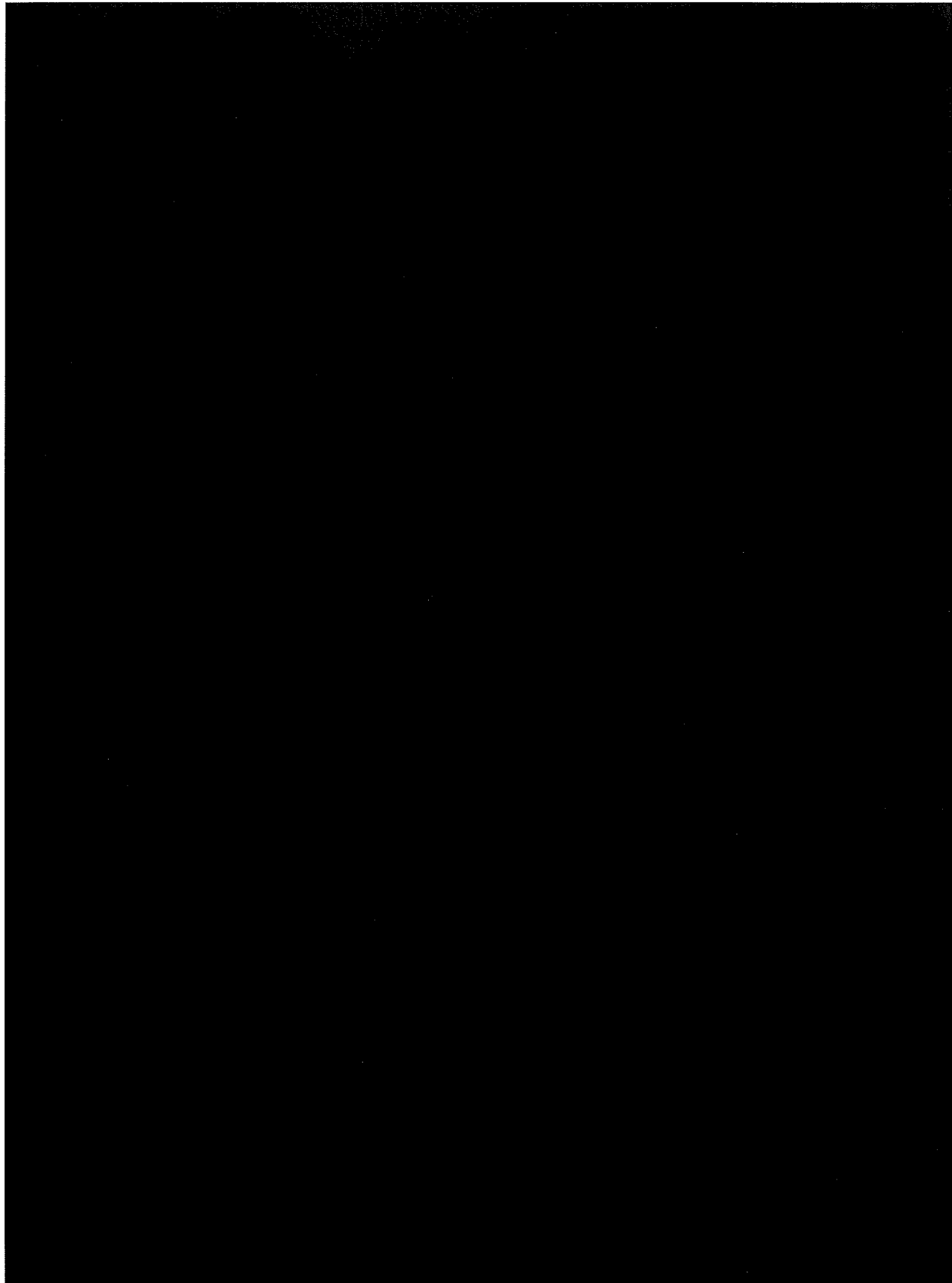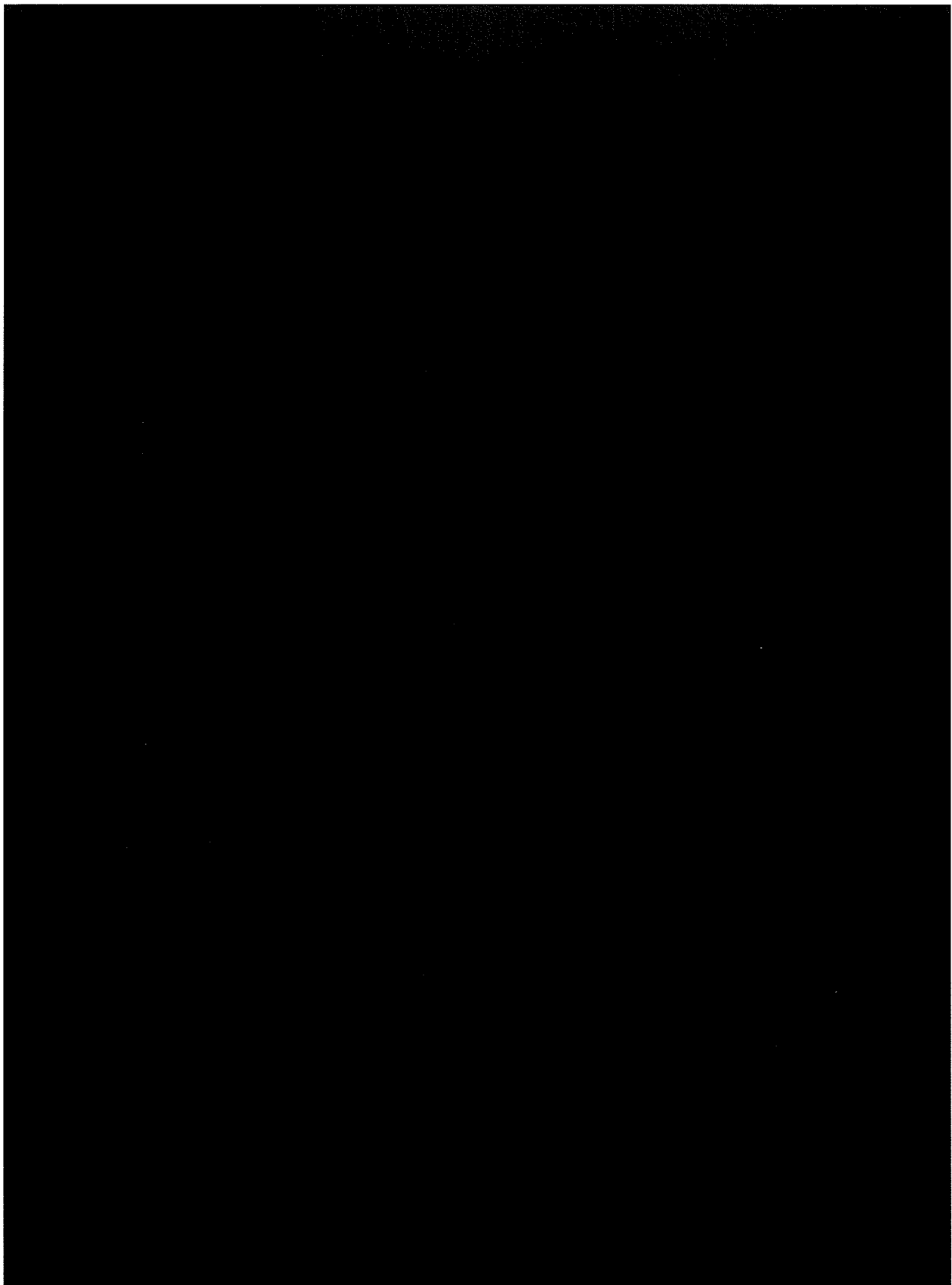
Appendix G: Overview of Physician Training Program

The WATCHMAN physician training program was used in the _Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device in Patients with Atrial Fibrillation versus Long Term Warfarin Therapy (PREVAIL)_ study. The training program described within this section includes all elements used during physician training for the PREVAIL study and the following additions:

- New echo simulation training with multiple anatomies
- New procedure simulation training with multiple cases
- Inclusion of "live taped cases" during the professional training event
- Optional physician proctoring during initial cases performed at a new users' site

The physician training program contains multiple elements including didactic training, imaging training, training in patient selection, device selection, complication management, and optional physician proctoring and meets the requirements recommended at the April 23, 2009 meeting of the Circulatory System Devices Panel. The training is based on the current Directions for Use (DFU) which includes indication, contraindications, warnings, precautions, and procedural steps.

Individual physicians and/or the collective physician-team must be proficient in transseptal skills prior to entering the WATCHMAN Training Program. Physicians will be required to provide BSC with documentation stating that they are experienced at and are routinely performing transseptal punctures.

The key elements of the WATCHMAN physician training program are:

1. Phase I: Pre-Study Review
   a. Pre-Study Review including a written workbook and online exam
   b. Online Case Review: 5 online interactive WATCHMAN implantation cases
2. Phase II: Attendance at a Professional Training Event conducted by WATCHMAN physician faculty
   a. Didactic review of WATCHMAN technology and procedural steps
   b. Case review by WATCHMAN physician faculty; the case observation will include at least 2 live and/or taped WATCHMAN left atrial appendage closure procedures
   c. Skills training
      i. Echo simulation training with multiple anatomies
      ii. Procedure simulation training with multiple cases
3. Phase III: Hands On Training (Initial WATCHMAN Implantation Procedures supported by a BSC Field Clinical Specialist (FCS) and by a physician proctor if requested)
   a. Team based training to include the implanting physician, Echocardiology staff (MD and technicians), and scrub technicians conducted by the FCS

      b. Didactic review of technology with operator and clinical staff conducted by the FCS
      c. Review of skills training conducted by the FCS
      d. Review of scheduled case conducted by the FCS or by the physician proctor (if attendance has been requested)
      e. Perform initial cases: implant procedures are supported by the FCS; physicians will have the option to request attendance by a physician proctor
      f. Review of first 2-3 cases with the implanting physician by the FCS to demonstrate that appropriate implant procedural steps were followed (documented on an implant worksheet)

4. Phase IV: FCS Supported Implantations
      a. Refine skills/techniques through performing a minimum of 8 additional cases supported by an FCS
      b. Review successful and challenging cases with an FCS to prepare for potential complications

WATCHMAN Physician Faculty

WATCHMAN physician faculty are physicians with extensive WATCHMAN experience who have completed a minimum of 30 WATCHMAN implant cases, and are regularly implanting WATCHMAN. Physician faculty are responsible for all training conducted at the Professional Training Events (Phase II).

Phase I: Pre-Study Review

The primary goals of the pre-study review are to provide physicians with knowledge about the:

- LAA Closure technology and procedure
- Appropriate patient selection criteria
- Various imaging techniques utilized to determine:
  - Appropriate device size
  - Proper access sheath placement
  - Device deployment
  - Device release criteria
  - Whether a patient is eligible to cease warfarin therapy
- Procedural steps and tips to avoid complications

In order to meet the goals described above, the pre-study review includes a workbook and associated required exam in addition to online cases and various online resources as described below:

- Workbook – LAA Closure Technology
  - Module 1: WATCHMAN® LAA Closure Technology
  - Module 2: WATCHMAN® Imaging Guidelines
  - Study Guide 2: WATCHMAN® LAA Closure Technology

- Exam: The exam includes an assessment of LAA selection (i.e., appropriate anatomy for device placement), device sizing and appropriate patient management and requires a score of 90% or greater before the physician will be allowed to begin implanting the device. The exam is administered on-line through Exam Builder which randomly selects 15 of the 32 questions for the student to be tested. The results are tracked electronically and explanations are given for each question that is asked. Physicians are allowed to take the test as many times as needed to become proficient with the material.
- Case Studies: 5 online interactive cases (based upon real cases) that require the physician to make a number of critical decisions correctly. The intent of the case review is to present an online interactive review of a safe and effective implant procedure and allows the physician to re-review subject matter in the context of a case study before moving to the next training phase.
- Online Resources
  - o Procedural steps and tips to avoid complications: This online audio and slide presentation provides training for the implant procedure by an experienced physician faculty member.
  - o Practice the Procedure: 3 additional interactive cases to illustrate the issues that a physician may encounter during a WATCHMAN procedure.
  - o Imaging Atlas: The imaging atlas provides a review of baseline, procedure and follow up imaging related to the WATCHMAN LAA Closure Technology.

Phase II: Attendance at a Professional Training Event

Professional Training Events are face to face training conducted by WATCHMAN physician faculty. This formal training includes didactic lectures, Computed Tomography Angiography (CTA) based 3D physical model, and computer based simulation. The computer simulation includes both echo simulation training and implant procedure simulation training with multiple anatomies for each.

Case observation and pre- and post-procedure review by a member of the physician faculty is required, and includes documented attendance at a minimum of 2 WATCHMAN left atrial appendage closure procedures or "taped live cases". Each case includes a standardized presentation on the WATCHMAN implantation procedure to include the following by a physician faculty member:

- Prior to procedure: a case pre-brief
- During the procedure: reinforcement of procedural steps, techniques, and recommendations
- After the procedure: a case debrief with question and answer session

Skills training is provided by physician faculty utilizing simulation and 3D physical models to provide the implanting physician with imaging training, device selection, procedural steps and tips to avoid complications.

Phase III: Hands On Training (Initial WATCHMAN Implantation Procedures)

This team-based training is conducted by the FCS and physician proctor (if requested) and includes the implanting physician, Echocardiology staff (MD and technicians), and scrub/lab

technicians. Prior to the case, a didactic review of the technology and skills training is conducted with the operator and clinical staff, followed by a review of the scheduled case(s):

    a. Team based training to include the implanting physician, Echocardiology staff (MD and technicians), and scrub technicians conducted by the FCS
    b. Didactic review of technology with operator and clinical staff conducted by the FCS
    c. Review of skills training conducted by the FCS
    d. Review of scheduled case conducted by the physician proctor (if attendance has been requested) or by the FCS
    e. Perform initial cases: implant procedures are supported by the FCS; physicians will have the option to request attendance by a physician proctor
    f. Review of first 2-3 cases with the implanting physician by the FCS to demonstrate that appropriate implant procedural steps were followed (documented on an implant worksheet)

The initial cases will be supported by an FCS as a reference for the safe and effective use of the device. Optional physician proctors will also be available to provide expert advice for at least the first 2-3 cases at an institution at request of the new user. Physician proctor responsibilities will include:

- Support initial case(s) at new user site, along with an FCS
- Provide hands-on review of device and sheath prior to procedure
- Review procedural steps prior to procedure
- Review baseline TEE images with new implanter to assist in choosing device size
- Provide verbal guidance to new implanter during procedure to ensure steps are followed
- Provide verbal discussion concerning release criteria prior to release of device
- Assist imaging team to obtain appropriate measurements of LAA prior to implant, as well as measurements of device post implant
- Provide guidance to imaging team as to direction and location of access sheath on various TEE images
- Provide guidance post implant on anticoagulation
- Provide contact information to new implanter for ongoing communication

The new user will formally review the first 2-3 cases with a FCS to demonstrate that appropriate implant procedural steps were followed (documented on an implant worksheet).

Phase IV: FCS Supported Implantations

Phase IV is intended to allow physicians to refine skills and techniques while performing a minimum of 8 additional cases. All implantations will be supported by an FCS until the physician(s) is certified as independent. Additional reviews of successful and challenging cases are performed during this time to prepare the physician for potential complications that might arise in future cases.

The implanting physician will formally review all cases performed during Phases III and IV with an FCS to demonstrate that appropriate implant procedural steps were followed (documented on an implant worksheet).

The implanting physician will be deemed independent (receive certification) and will be allowed to implant the WATCHMAN device on their own (without requiring presence of an FCS) after a minimum of 10 implant procedures and demonstration of transseptal puncture and device placement skills.

Physician faculty and/or physician proctors will also be available to new implanting physicians throughout training to review and / or discuss any questions or challenges they may have encountered in their initial WATCHMAN cases. This may include but not be limited to telephone consultation, sharing of images from cases, or other means to reinforce procedural techniques.

Documentation of Training and Certification

Records are kept to document training and certification for each physician. A validated custom database has been developed to track the following minimum requirements for certified independence:

1. Passing completion of online exam (Phase I)
2. Review of online cases (Phase I)
3. Participation in Professional Training Event (Phase II)
4. Completion of initial WATCHMAN implantation procedures, case reports are required prior to documentation in the database (Phase III)
5. Additional FCS supported implantations; case reports are required prior to documentation in the database (Phase IV)
6. Completion of at least 10 total cases (combined Phase III and IV)
7. Review of cases with FCS to demonstrate that appropriate implant procedural steps were followed (documented on an implant worksheet)

Upon completion and documentation of the items above, an Implanting Physician Training Record (checklist) is completed and signed by the implanting physician, FCS, and the WATCHMAN Education Manager. Certification is granted upon signed completion of this training record.

Appendix H: Patient Guide

The subsequent pages contain the WATCHMAN Left Atrial Appendage Closure Device Patient Guide.

WATCHMAN® Left Atrial Appendage Closure Device

Patient Information Guide

You have recently had a WATCHMAN Left Atrial Appendage Closure Device implanted in the left atrial appendage (LAA) of your heart. The following information is important for you to know, including the possible risks associated with having a WATCHMAN Closure Device implanted, along with medication recommendations and questions you may have about your device.

WATCHMAN Left Atrial Appendage Closure Device

The WATCHMAN Left Atrial Appendage Closure Device is a permanent implant designed to keep harmful blood clots from entering your blood stream, potentially causing a stroke. It is made of materials that are common to many medical devices. The device is designed to be permanently implanted at or slightly distal to the ostium (opening) of the LAA to trap potential emboli before they exit the LAA.
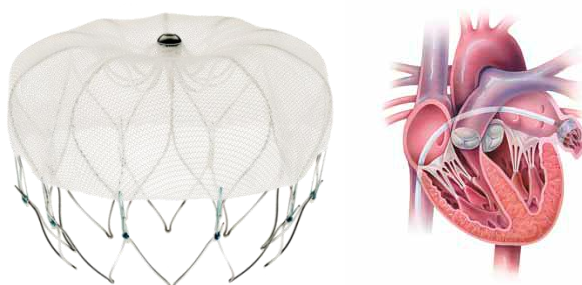
Potential adverse events (in alphabetical order) which may be associated with the use of closure devices in the LAA include but are not limited to:

- Accidental heart puncture causing fluid collection in the heart sac (pericardial effusion) which may lead to increased pressure in the heart sac (tamponade)
- Air Embolism
- Allergic reaction to the contrast dye, anesthetic, WATCHMAN material, or surgical equipment
- Anemia Requiring Transfusion
- Arrhythmias
- AV (Arteriovenous) Fistula
- Bleeding or throat pain from the TEE (TransEsophageal Echo**)** probe
- Blood clot or air bubbles in the lungs or other organs
- Bruising (hematoma) or fluid collection (seroma) at the catheter insertion site
- Clot formation on the WATCHMAN® Closure Device

- Cranial Bleed
- Death
- Device Embolization
- Device Misplacement
- Device Thrombus
- Excessive Bleeding
- Gastrointestinal Bleeding
- Groin Puncture Bleed
- Hypotension
- Inability to Move or Retrieve Device
- Infection/Pneumonia
- Irregular heartbeats
- Major Bleed Requiring Transfusion
- Pleural Effusion
- Pneumothorax
- Post Procedure Anesthesia Effects
- Pseudoaneurysm
- Pulmonary Edema
- Pulmonary Vein Obstruction
- Some additional events that may be expected in catheterization procedures include:
- Stroke – Hemorrhagic
- Stroke - Ischemic
- Systemic Embolism
- TEE (TransEsophageal Echo) Complications (throat pain, bleeding)
- Thrombosis
- Thrombus at Septal Puncture
- Transient Ischemic Attack (TIA)
- Valvular or vascular damage
- Vasovagal Reactions

There may be other potential adverse events that are unforeseen at this time.

Medications

Your doctor has prescribed medication to thin the blood and prevent blood clots from forming. Current guidelines recommend anticoagulation with Warfarin (Coumadin®) to thin the blood and delay clotting (coagulation) in patients with AF. A test called the International Normalized Ratio (INR) is used to assess the time it takes for the blood to clot and to determine the correct dose of warfarin. Too high a dose increases the risk of bleeding. Too low a dose increases the risk of clotting. Because the correct warfarin dose may change over time, it's important to test the INR at regular intervals. Your doctor will also have you take aspirin after your device has been implanted. After your device has been in place for a minimum of 45 days, your doctor *may* stop your warfarin medication. If your doctor chooses to do so, he/she will prescribe clopidogrel and may increase your aspirin dose.

It is extremely important to follow your medication regimen. If you stop taking these medications before being instructed to do so by your doctor, the chances of blood clot formation, subsequent stroke or even death are increased.

If surgery or dental work is recommended which would require you to stop taking these medications prematurely, you and your doctors should carefully consider the risks and benefits of this additional surgery or dental work versus the possible risks from early discontinuation of these medications.

If you do require premature discontinuation of these medications because of significant bleeding, then your doctor will be carefully monitoring you for possible complications. Once your condition has stabilized, your doctor will probably put you back on these medications.

After the Procedure

After the device is implanted, you will rest in the hospital where you can be monitored closely as you begin to recover. It may be one or more days before you are discharged from the hospital.

Activity

- Follow your doctor's guidelines.
- Return to normal activities gradually, pacing your return to activity as you feel better. Check with your doctor about strenuous activities.
- Let your doctor know about any changes in lifestyle you make during your recovery period.
- Report side effects from medications immediately. These may include headaches, nausea, vomiting or rash.
- Do not stop taking your medications unless you are asked to stop by the doctor who implanted your device.
- Keep all follow-up appointments, including laboratory blood testing.
- Carry your WATCHMAN® Closure Device Implant Card at all times. If you receive dental or medical care or report to an emergency room/center, show your Closure Device Implant Card.

Frequently Asked Questions

Can the WATCHMAN Closure Device move or rust?

Once positioned by your physician, the device should not move on its own. It is manufactured so it will not rust.

Can I walk through metal detectors with the WATCHMAN Closure Device?

Yes, without any fear of setting them off.

How soon can I resume normal daily activities?

The majority of people return to normal daily activities within a few days following the procedure.

What if I experience pain?

If you experience pain, immediately inform your doctor or the center where the procedure was performed.

What if I miss taking my medication?

Call your doctor.

Can I undergo MRI or scanner testing with the WATCHMAN® Closure Device?

MRI safety testing has shown that the WATCHMAN Left Atrial Appendage Closure Device is MR Conditional and that a patient with a WATCHMAN Closure Device may safely undergo an MRI scan under certain conditions listed on the WATCHMAN Closure Device Implant Card. Prior to undergoing an MRI scan, inform your doctor or MR technologist that you have a WATCHMAN Left Atrial Appendage Closure Device.

Indications, contraindications, warnings and instructions for use can be found in the labeling supplied with each product. CAUTION: Federal (U.S.A.) law restricts these products to sale by or on the order of a physician.

Boston Scientific Corporation
One Boston Scientific Place
Natick, MA 01760-1537
1.888.272.1001
www.bostonscientific.com/watchman
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WATCHMAN® Closure Device Implant Card

WATCHMAN Left Atrial Appendage Closure Device
Boston Scientific Corporation
One Boston Scientific Place
Natick, MA 01760-1537USA
USA Customer Service 888-272-1001
www.bostonscientific.com/watchman

Device: WATCHMAN Left Atrial Appendage Closure Device
Patient Name:
Date of Implant:
Device Lot #:
Implanting Physician:
Hospital:
Contact information:

If you require a magnetic resonance imaging (MRI) scan, tell your doctor or MRI technician technologist that you have a left atrial appendage Closure Device. Non-clinical testing has demonstrated the WATCHMAN Closure Device is MR Conditional. A patient with the Closure Device can be scanned safely under the following conditions:

- Static magnetic fields of 1.5 Tesla or 3 Tesla
- Spatial gradient field of 2500 Gauss/cm or less
- The maximum whole body averaged specific absorption rate (SAR) shall be limited to 2.0 W/kg (normal operating mode only) for 15 minutes of scanning
- Normal operating mode of the MRI scanner

The WATCHMAN LAA Closure Device should not migrate in this MRI environment.
MR imaging within these conditions may be performed immediately following the implantation of the device. MR image quality may be compromised if the area of interest is relatively close to the WATCHMAN device. Optimization of MR imaging parameters is recommended. This device has not been evaluated to determine if it is MR Conditional beyond these parameters.

PLEASE CARRY YOUR CARD AT ALL TIMES.

Your doctor has prescribed medication to thin the blood and prevent blood clots after your implant. It is extremely important to follow the medication regimen as prescribed by your doctor. Before considering any surgery or dental work which would require you to stop taking these medicines early, you and your doctors should consider the risks from premature discontinuation of these medications**. For questions regarding your Left Atrial Appendage Closure Device or other procedures (e.g., MRI), please contact your implanting doctor.**

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Appendix I: Post-approval Study

In line with expected FDA conditions of approval requirements for Left Atrial Appendage Closure Devices, a post-approval study of the WATCHMAN LAAC Therapy will be conducted after the device is approved for use in the United States. A synopsis of the proposed study design is presented below.

WATCHMAN Post Approval Study Summary

Objective: The WATCHMAN Post Approval Study is designed to assess long term safety and effectiveness outcomes associated with the use and implantation of the WATCHMAN LAAC Therapy in a routine clinical setting.

Intended Use: The WATCHMAN is a percutaneous, transcatheter closure device intended for non-surgical closure of the left atrial appendage.

Test Device: WATCHMAN LAAC Therapy

Device Sizes: 21mm, 24mm, 27mm, 30mm, 33mm

Study Design: This is a non-randomized study that will prospectively enroll subjects newly implanted with the WATCHMAN device and retrospectively enroll subjects who were previously implanted with the WATCHMAN device in the Continued Access to PROTECT (CAP), PREVAIL, or Continued Access to PREVAIL (CAP2) clinical studies (IDE G020312).

Planned Number of Subjects: Up to 1000 Subjects (chosen to establish a 95% confidence interval for the occurrence of rare events)

- Up to 600 retrospective (from existing WATCHMAN trials still in follow-up)
- Up to 500 prospective

Planned Number of Centers: Up to 100 sites located in the United States

Primary Endpoint: Descriptive statistics will be used for baseline, procedure and follow-up data collected through the study.

Method of Assigning Patients to Treatment: All subjects will be assigned the same treatment, as this is a single-arm study.

Follow-Up Schedule: Subjects will be followed at intervals of 45 days, 12 months and annually thereafter through 5 years post implant.

Study Duration: Subjects will be followed through 5 years post implant. It is anticipated that the enrollment period will occur over a period of two years.

Required Medication Therapy: Warfarin, aspirin, clopidogrel, ticlopideine, prasugrel, heparin, antibiotics, as applicable and outlined within the protocol.

Key Inclusion Criteria: Patients who meet all of the following criteria may be given consideration for inclusion in this clinical investigation, provided no exclusion criteria are met.
1. The patient is 18 years of age or older
2. The patient has non-valvular atrial fibrillation
3. The patient has a calculated $CHADS_2$ score of 2 or greater; Subjects with a $CHADS_2$ score of 1 may be included if any of the following apply:
    a. The patient is a female age 75 or older
    b. The patient has a baseline Left Ventricular Ejection Fraction (LVEF) $\geq$ 30% and < 35%
    c. The patient is age 65-74 <u>and</u> has diabetes or coronary artery disease
    d. The patient is age 65 or greater <u>and</u> has documented congestive heart failure
4. The patient is eligible for post implant warfarin therapy
5. Willing and able to provide written informed consent or have written informed consent provided by a legal representative
6.

Key Exclusion Criteria: Patients who meet any of the following criteria will be excluded from this clinical study.
1. The patient has intracardiac thrombus or dense spontaneous echo contrast as visualized by peri-procedural TEE.
2. The patient has a history of atrial septal repair or has an ASD/PFO device
3. The patient's LAA anatomy will not accommodate a WATCHMAN device
4. The patient has any contraindications for other percutaneous catheterization interventions due to patient size (i.e. too small for TEE probe, catheter size, etc.) or condition (i.e. active infection, bleeding disorder, untreated ulcer, etc.)
5. The patient is contraindicated or allergic to aspirin
6. The patient requires long term warfarin therapy for a condition other than atrial fibrillation.
7. The patient has a life expectancy of less than one year